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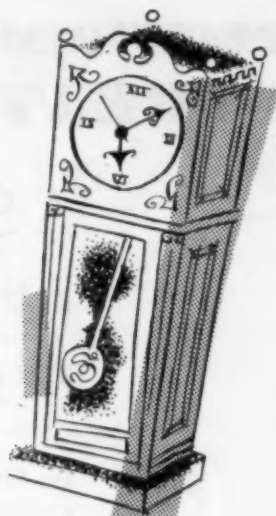
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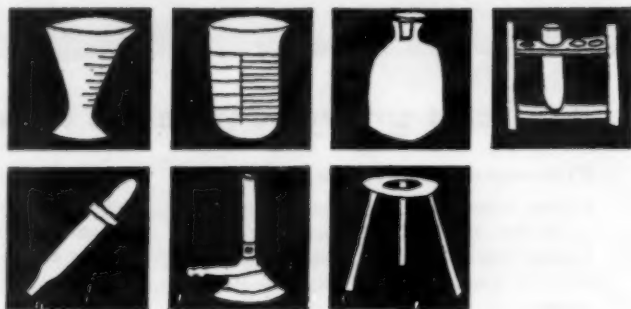
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Ferrous sulfate exsic. (3 gr.)	200.0 mg.
Vitamin B ₁₂ U.S.P. (crystalline)	10.0 mcg.
Gastric mucosa (dried)	100.0 mg.
Desiccated liver substance, N.F.	100.0 mg.
Folic acid U.S.P.	0.67 mg.
Thiamine mononitrate (B ₁)	10.0 mg.
Vitamin C (ascorbic acid)	50.0 mg.

No. 340 — Bottles of 100 and 1,000.

SUGGESTED DOSAGE:

1 or 2 capsules three times daily. Preferably taken with food.

NEW YORK, N. Y.



MONTREAL, CANADA

compare before you prescribe

modern criteria of good digitalis therapy

- 1** pure active principle
- 2** complete absorption
- 3** rapid onset of action
- 4** smooth, even maintenance
- 5** frequent dosage readjustment unnecessary
- 6** virtual freedom from gastric upset

digitaline nativelle®

conforms to the rigid criteria of a modern cardiotonic and provides oral, I.M., and I.V. forms for flexibility of dosage

compare *then prescribe...*

DIGITALINE NATIVELLE

—the original pure crystalline digitoxin

Consult your Physicians' Desk Reference for dosage information.

VARICK PHARMACAL COMPANY, INC.

(Division of E. Fougera & Co., Inc.)

75 Varick Street, New York 13, N. Y.

NOW the safest agent
yet developed for
decisive control of **BLOOD PRESSURE**
with **5** important firsts

UNITENS

brand of cryptenamine

Unitensin is recommended for the patient who needs more than tranquilizing effects. It produces positive, sustained falls in blood pressure.

This is what Unitensin Tablets do . . . and with unparalleled safety

Summary of Case Histories-Series A*

Age—Sex	BP—mm. Hg. BEFORE	BP—mm. Hg. AFTER
54—M	190/115	140/90
37—M	200/130	130/85
48—M	230/140	140/100
46—M	220/140	180/110
41—M	210/140	155/110
43—M	200/120	160/110
26—M	230/130	180/120
44—M	220/130	175/120
46—M	220/120	162/90

These patients experienced sustained control of blood pressure levels over prolonged periods of time.

(Write for complete clinical data, including case histories.)

*Personal communication to Ineth, Reister & Company.

FIRST IN MAINTAINING DECISIVE BLOOD PRESSURE CONTROL

The sole therapeutic agent in Unitensen Tablets is cryptenamine—a potent blood pressure lowering alkaloid fraction isolated by the research staff of Irwin, Neisler & Company. In the majority of cases (see chart at left), cryptenamine will lower blood pressure decisively, and will control blood pressure at the lower levels for prolonged periods of time.

FIRST IN SAFETY

Unitensen Tablets exert a central action on the blood pressure lowering mechanism. Circulatory equilibrium is not disrupted. Improved circulation and improved work of the heart are often attained, *along with the decisive fall in blood pressure.*

Unitensen Tablets have no sympatholytic or parasympatholytic action. Ganglionic blocking does not occur. Unitensen Tablets *do not* cause postural hypotension and collapse, an ever-present risk with other potent blood pressure lowering drugs. Renal function is *not* impaired.

FIRST WITH DUAL ASSAY

Unitensen is biologically standardized twice, first for hypotensive response and, second, for side effects (emesis) in the dog so that a safe therapeutic range between the two is assured. In extensive clinical trials only a few isolated cases exhibited occasional vomiting.

Unitensen Tablets do not cause the serious side effects common to widely used synthetic hypotensives. Unitensen Tablets can be given over long periods of time with entire dependability. Cumulative effects have not been noted.

FIRST IN SIMPLE DOSAGE

Start with 2 tablets daily, given immediately after breakfast and at bedtime. If more tablets are needed, include an afternoon dose at 1 or 2 p.m.

FIRST IN ECONOMY

Because of lower dosage, Unitensen Tablets save your patients $\frac{1}{3}$ to $\frac{1}{2}$ over the cost of other potent blood pressure lowering agents.

Each Unitensen Tablet contains: Cryptenamine* 2 mg.†
(as the tannate salt)

*Ester alkaloids of *Veratrum viride* obtained by an exclusive Irwin-Neisler nonaqueous extraction process. †Equivalent to 260 Carotid Sinus Reflex Units.

IRWIN, NEISLER & COMPANY

DECATUR, ILLINOIS

EN[®]

TANNATE TABLETS

Bottles of 50, 100,
500 and 1000.

For the many thousands of patients with essential hypertension, there is new hope for longer, happier lives. RESERPOID* (Upjohn brand of reserpine) is the active, pure alkaloid of Rauwolfia serpentina. In just 1/1000 mg., Reserpoid matches the potency of 1

mg. of the whole root... Reserpoid carries non-hypnotic sedation and bradycardic action along with its principal antihypertensive effect. It is a persistently pleasant drug: usually even before the pressure falls, a sense of calm settles over the anx-

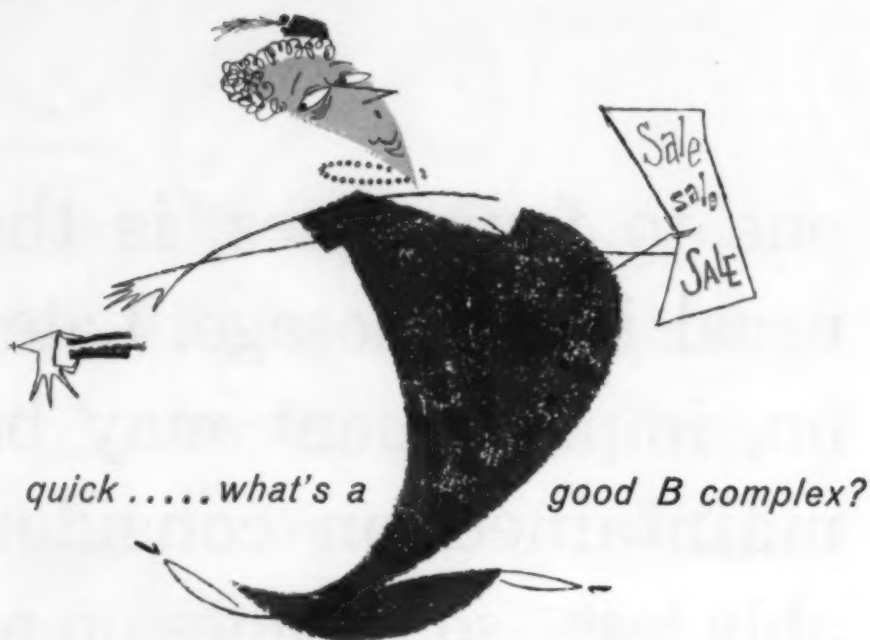
ious and irritable hypertensive. Lowering of the pressure is gradual, which gives the patient a week or more to adjust to the new levels. Reserpoid acts centrally upon the autonomic nervous system. It is not a ganglionic blocking agent, does not induce

postural hypotension . . . Reserpoid has no presently defined contraindications. It is ideal for the "average" case—that large group of mild and moderate hypertensives who have symptoms, but no demonstrable pathology. In severe hypertension with advancing vas-

cular damage, Reserpoid is valuable in augmenting and stabilizing the effects of other, more drastic drugs—making their smaller dosage possible. Reserpoid therapy is not encumbered by the difficulties of delicate titration. Just 1 mg. of Reserpoid daily, taken in

one to four doses, is the usual initial dosage. Later on, improvement may be maintained on considerably less—sometimes on as little as 0.1 mg. per day. Reserpoid is available in 0.1 mg. and 0.25 mg. scored tablets, in bottles of 100 and 500, at all R_x pharmacies.

The Upjohn Company, Kalamazoo, Michigan



SUR-BEX[®]

(Abbott's Vitamin B Complex Tablets)

or SUR-BEX with Vitamin C

(Contains 150 mg. of ascorbic acid in addition to the B complex factors below)

just 1 SUR-BEX tablet a day supplies:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
→ Vitamin B ₁₂ (as vitamin B ₁₂ concentrate)	2 mcg.
Pantothenic Acid (as calcium pantothenate)	10 mg.
Liver Fraction 2, N.F.	300 mg.
Brewer's Yeast, Dried	150 mg.



408577

Please Mention this Journal when writing to Advertisers

S.K.F.'s widely acclaimed new antihistamine preparation



chlorphenpyridamine maleate



brand of sustained release capsules

for continuous and sustained relief of allergic disorders

"BEST METHOD AVAILABLE"

30 patients, severe allergic symptoms. "It is our belief that this drug used in this form provides the best method available for antihistamine medication."

—ROGERS, H.L.: Ann. Allergy 12:266 (May-June) 1954.

"HEARTILY ENDORSED"

357 patients, allergic disorders. "66% of the group obtained excellent symptomatic relief; 16% obtained good relief; 11%, fair relief; 7% obtained no relief."

"[Teldrin' Spansule] capsules, aside from their long-acting property and low incidence of side effects, provide an obvious advantage of patient acceptance. . . . they were heartily endorsed by nearly all patients."

—GREEN, M.A.: Ann. Allergy 12:273 (May-June) 1954.

"MOST USEFUL"

128 patients, hay fever. "From these results, it is believed that the [Teldrin' Spansule] capsule is the most useful antihistaminic preparation currently available as adjuvant therapy in treating hay fever."

—MULLIGAN, R.M.: J. Allergy 25:358 (July) 1954.

around-the-clock protection

Adults and Older Children: One capsule (12 mg.) q12h.

Younger Children: One capsule (8 mg.) q12h.


made only by

Smith, Kline & French Laboratories, Philadelphia

the originators of sustained release oral medication

*T.M. Reg. U.S. Pat. Off.

Patent Applied For



*control of
salt-retention
edema*

maintained by

CUMERTILIN[®]

[Brand of Mercumatilin]

TABLETS

effective oral diuretic

**...with no significant
gastrointestinal irritation**

In a recent study,¹ CUMERTILIN Tablets alone proved effective and well tolerated in maintaining cardiac compensation in most ambulant patients with congestive heart failure. Long-term treatment for periods ranging up to 658 days was accomplished "with no significant gastrointestinal reactions."

Dosage is 1 to 3 tablets daily as required.

Supplied as orange tablets, each containing 67.7 mg. CUMERTILIN (equivalent to 20 mg. each of mercury and theophylline). Also available as CUMERTILIN Sodium Injection, 1- and 2-cc. ampuls, 10-cc. vials.

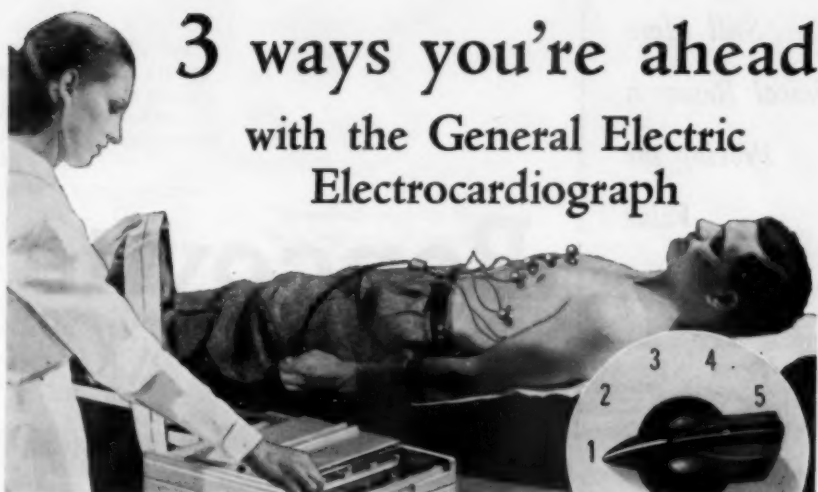
Samples? Just write to:

Endo[®]

ENDO PRODUCTS INC.
Richmond Hill 18, New York

1. Pollack, B. E., and Pruitt, F. W.: Am. J. Med. Sci., 226:172, 1953.

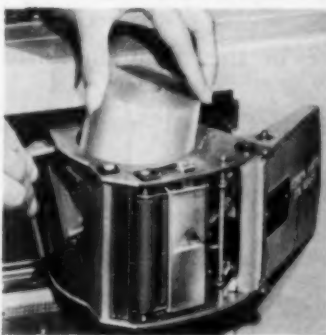




1 Exclusive switch selection for simpler, faster recordings

Without changing electrodes, you can take up to 30 leads, including six chest positions.

Once the patient electrodes are in place, you can take leads 1, 2, 3, aVR, aVL, aVF, and the 1 to 6 positions at V, CR, CL and CF by merely turning selector switches.



2 New paper drive for easier loading, greater accuracy

Using a new type of roller and a synchronous motor, General Electric assures uniform paper speed for accurate measurement of conduction times. Loading is simple — nothing to disassemble. Just flip open hinged door . . . place paper roll on spindle . . . thread through simple guides . . . and snap unit back in place. *All in a few seconds.*



3 New cabinet design for easier operation and carrying, added safety

Dual hinged covers open at a touch, making recessed controls immediately accessible. Cover supports no weight when unit is carried — handle attaches to main case. For all the facts on the DWB Cardioscribe, see your G-E x-ray representative. Or write X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin, for Pub. M-95.

Progress Is Our Most Important Product

GENERAL  ELECTRIC

*Still More
Clinical Research
Proving the
Value
of*

Roncovite

in anemia therapy—

The rapidly expanding volume of clinical research continues to prove the effectiveness and safety of Roncovite in the common forms of anemia.* These clinical studies of the effect of cobalt-iron have produced gratifying results in several types of anemia.

**AREAS OF
CLINICAL STUDY
INCLUDE:**

iron deficiency anemia
anemia in chronic infection
anemia in pregnancy
anemia in infants and prematures

Cobalt in therapeutic dosage exerts a specific erythropoietic effect on the bone marrow. Roncovite provides the supplemental iron to meet the need of the resulting accelerated hemoglobin formation.

—and from 1954 clinical reports

"We agree with Waltner (1930) and Virdis (1952) that iron should be given together with cobalt to obtain the most satisfactory results."¹

"Evidence suggests that iron and cobalt provide the most effective hematinic for pregnant women."²

"The babies were closely observed daily for ill effects of the medication while at the premature unit and when they returned for check-ups. None of them showed harmful effects despite the large doses."³

SUPPLIED

RONCOVITE TABLETS

Each enteric coated, red tablet contains:
Cobalt chloride 15 mg.
Ferrous sulfate exsiccated 0.2 Gm.

RONCOVITE DROPS

Each 0.6 cc. (10 drops) provides:
Cobalt chloride 40 mg.
(Cobalt . . . 9.9 mg.)
Ferrous sulfate 75 mg.

RONCOVITE-OB

Each enteric coated, red capsule-shaped tablet contains:
Cobalt chloride 15 mg.
Ferrous sulfate exsiccated 0.2 Gm.
Calcium lactate 0.9 Gm.
Vitamin D 250 units

DOSAGE

One tablet after each meal and at bedtime; 0.6 cc. (10 drops) in water, milk, fruit or vegetable juice once daily for infants and children.

*Bibliography of 192 references available on request.

1. Coles, B.L., and James, U.: The Effect of Cobalt and Iron Salts on the Anaemia of Prematurity, Arch. Disease in Childhood 29:85 (1954).
2. Holly, R.G.: The Value of Iron Therapy in Pregnancy, Journal-Lancet 74:211 (June) 1954.
3. Quilligan, J.J., Jr.: Effect of a Cobalt-Iron Mixture on the Anemia of Prematurity, Texas St. J. Med. 50:294 (May) 1954.

Roncovite

The original, clinically proved, cobalt-iron product.

LLOYD

BROTHERS,

INC. Cincinnati 3, Ohio

In the Service of Medicine Since 1870

Enriched Bread in Dietary Planning



BECAUSE of its nutritional, dietetic, and physiologic values, enriched bread simplifies in many ways the organization of dietaries suited to the special requirements of patients.



FOR THE SURGICAL PATIENT...

The first solid food after surgery is toasted enriched bread, slightly buttered. This practice

has become a tradition—almost a ritual—because of the very nature of toast. It is bland, easily digested, and yields little inert residue. Its golden, warm appearance is pleasing to the eye; its mild taste appeals to the palate. Its nutrient energy plays a role in the physiologic and psychologic re-awakening of metabolic processes depressed under the "nothing by mouth" conditions immediately following surgery. With increasing tolerance for food it becomes an important component of the soft diet and later of the therapeutic diet.¹ Its valuable protein, B vitamins, iron, calcium and calories help the patient to regain nutritional efficiency.



FOR THE CONVALESCENT...

Enriched bread figures prominently in the dietary regimen in convalescence after acute infections, other serious illness, or trauma.

Supplying 13 grams of high grade protein per 5½ ounces (estimated average

daily consumption), enriched bread makes an important contribution to the daily protein need. Its protein, comprising flour, milk, and yeast proteins, functions in the healing of wounds and in the rebuilding of wasted tissues.² In addition, 5½ ounces of enriched bread supplies on the average 0.37 mg. of thiamine, 0.23 mg. of riboflavin, 3.4 mg. of niacin, 4.1 mg. of iron, 137 mg. of calcium, and 418 calories.



FOR THE CHRONICALLY ILL...

In the formulation of palatable and nutritious menus for the debilitated, chronically ill, the advantages of enriched bread serve well.

In anorexia, enriched bread or toast stimulates the appetite. It is easily masticated and readily digested, features particularly important for elderly patients. Its favorable textural influence within the alimentary tract³ promotes good utilization of ingested foods.

1. The Committee on Dietetics of the Mayo Clinic: *Mayo Clinic Diet Manual*, ed. 2, Philadelphia, W. B. Saunders Company, 1954.

2. Sherman, H.C.: *Chemistry of Food and Nutrition*, ed. 8, New York, The Macmillan Co., 1952, pp. 212, 599.

3. Sherman, H.C.: *The Nutritional Improvement of Life*, New York, Columbia University Press, 1950, p. 133.



The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

AMERICAN BAKERS ASSOCIATION

30 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

for "This Wormy World"



SYRUP OF

'ANTEPAR'*

effective against

PINWORMS

and

ROUNDWORMS

'Antepar' is a well-tolerated, fruit-flavored Syrup—pleasant to take.

*SYRUP OF 'ANTEPAR' Citrate brand Piperazine Citrate, containing the equivalent of 100 mg. piperazine hexahydrate per cc.

Bottles of 4 fluid ounces and 1 pint



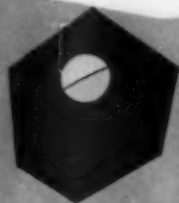
BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe 7, N. Y.

Combination tranquilizer-antihypertensive

*especially for
moderate and severe
essential hypertension . . .*

T.M.
Serpasil-Apresoline®
hydrochloride

(RESERPINE AND HYDRALAZINE HYDROCHLORIDE CIBA)



Combined in a Single Tablet

- The tranquilizing, bradycrotic and mild antihypertensive effects of Serpasil, a pure crystalline alkaloid of rauwolfia root.
- The more marked antihypertensive effect of Apresoline and its capacity to increase renal plasma flow.

Each tablet (scored) contains 0.2 mg. of Serpasil and 50 mg. of Apresoline hydrochloride.

C I B A
SUMMIT, N. J.

02 SEP 68

*This new antibacterial
really tastes good —*

An antibacterial that really
tastes good -- Gantrisin (acetyl)
Pediatric Suspension 'Roche.'

It has the same advantages as
Gantrisin 'Roche' but the flavor
is far superior. Children like
to take Gantrisin®(acetyl)
Pediatric Suspension because of
its pleasant raspberry flavor.

External eye infections...

Gantrisin Ophthalmic Solution and Ointment

Ear infections...

Gantrisin Ear Solution

Nasal infections...

Gantrisin Nasal Solution (with Neo-Synephrine)

Vaginal infections...

Gantrisin Cream for vaginal use

Systemic and urinary infections...

Gantrisin Tablets

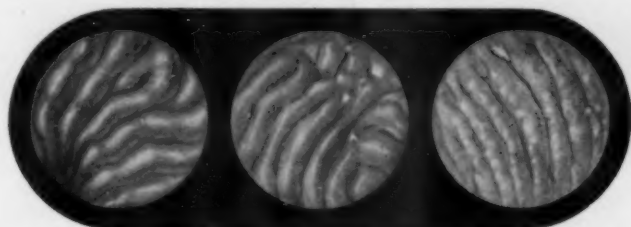
Parenteral antibacterial therapy...

Gantrisin Ampuls

Pediatric infections...

Gantrisin® (acetyl) Pediatric Suspension, Syrup

"...the gastric secretion is the immediate agent of mucosal tissue digestion. . . . Opposed to this stands the defensive factor . . . the two-component mucous barrier"¹ [the protecting layer of mucus and the mucosal epithelium].



Rotational gastrosopic views showing coating effect 1½ hours after administration of Amphojel.²

Causation — key to treatment in peptic ulcer

Through *topical* action alone, AMPHOJEL contends with the local causes of ulcer—aggressive acidity coupled with impairment of the wall defenses. Providing a dual approach, AMPHOJEL combines two aluminum hydroxide gels, one reactive, one demulcent. The reactive gel combats the attacking factor in ulcer by promptly buffering gastric acid. The demulcent gel promotes healing of the denuded mucosa by forming a viscous, protective coagulum.

AMPHOJEL—nonsystemic, nontoxic—provides time-proved *fundamental* therapy.



AMPHOJEL®
ALUMINUM HYDROXIDE GEL

Supplied: Liquid, bottles of 12 fluidounces
Tablets, 5 grain, boxes of 30, bottles of 100;
and 10 grain, boxes of 60 and 1000

References: 1. Hollander, F.: Arch. Int. Med. 93:107 (Jan.) 1954
2. Deutsch, E.: Scientific Exhibit, Gastroscopy,
Interim Session A.M.A., St. Louis, December, 1953



Philadelphia 2, Pa.

For assured dependability
in Digitalis administration



Physiologically Standardized
Pil. Digitalis (Davies, Rose)

0.1 Gram (approx. $1\frac{1}{2}$ grains)

Comprise the entire properties of the leaf.

Clinical samples sent to physicians on request.

Davies, Rose & Company, Limited

Boston 18, Massachusetts

RHEUMATIC PAIN

OSTEOARTHRITIS

ACUTE RHEUMATIC FEVER

GOUT

RHEUMATOID ARTHRITIS

MYALGIA

NEURALGIA

*these people are safer on***ARMYL**

Highest vitamin C content of any synergistic salicylate compound

Armyl, with its contained vitamin C, counteracts the increased excretion of this vitamin observed during salicylate therapy, and provides the antihemorrhagic protection of ascorbic acid.

Armyl tablets produce higher plasma levels of salicylate for more efficient results. Therefore, smaller doses can be given.

Enteric-coated Armyl provides marked relief of pain with minimal untoward side effects associated with salicylate therapy.

Each enteric-coated tablet contains:

Sodium Salicylate (5 gr.) 0.3 Gm.

Sodium Para-aminobenzoate (5 gr.) 0.3 Gm.

Ascorbic Acid (50 mg.) 0.05 Gm.

DOSE: Average adult dose, 2 tablets 4 times daily. Dosage may be increased considerably in acute conditions. Children's dose in proportion to age.

Also available ARMYL with $\frac{1}{8}$ gr. Phenobarbital
 ARMYL Sodium-Free
 ARMYL Sodium-Free with $\frac{1}{8}$ gr. Phenobarbital

Each of these products provides all the clinical benefits of Armyl.

Supplied in bottles of 100



THE ARMOUR LABORATORIES A DIVISION OF ARMOUR AND COMPANY • CHICAGO 11, ILLINOIS

Here are the

Therapeutic Nutrition

By Herbert Halden and Seymour L. Haberman
in collaboration of the Committee on Therapeutic Nutrition and Nutrition Research Council

National Academy of Sciences—
National Research Council

Publication 234



*Therapeutic Nutrition,
Publication 234,
National Research Council*



Formula
Products



Vitamin
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Please Mention this Journal when writing to Advertisers

new and clearly defined National Research Council Standards* for vitamin therapy



to safeguard and maintain vitamin adequacy

PANALINS

N.R.C. STANDARD *maintenance* VITAMIN CAPSULE

Each Panalins capsule supplies:

Thiamine.....	2 mg.
Riboflavin.....	2 mg.
Niacinamide.....	20 mg.
Ascorbic acid.....	50 mg.
Calcium pantothenate.....	5 mg.
Pyridoxine.....	0.5 mg.
Folic acid.....	0.25 mg.
Vitamin B ₁₂	2 mcg.
Vitamin A.....	5000 units
Vitamin D.....	400 units

Bottles of 100 and 500.



1 or 2 Panalins capsules daily for:

persons on inadequate or restricted diets
irregular eaters
convalescents
growing children
adolescents
persons undergoing mild illness or stress

for vitamin therapy in stress situations

PANALINS-T

N.R.C. STANDARD *therapeutic* VITAMIN CAPSULE

Each Panalins-T capsule supplies:

Thiamine.....	10 mg.
Riboflavin.....	10 mg.
Niacinamide.....	100 mg.
Calcium pantothenate.....	20 mg.
Pyridoxine.....	2 mg.
Folic acid.....	1.5 mg.
Ascorbic acid.....	300 mg.
Vitamin B ₁₂	4 mcg.

Bottles of 30 and 100.



1 or 2 Panalins-T capsules daily for:

the severely ill
the chronically ill
surgical patients
burned or injured patients
vitamin-depleted patients
persons under any severe stress

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A.



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is for
Reserpine
now combined
with
VERALBA*
for simpler,
safer, two-way
hypertension
therapy

VERALBA-R

PROTOVERATRINES A AND B WITH RESERPINE

In the treatment of mild, moderate, or malignant hypertension, combination of the protoveratrines with reserpine in VERALBA-R offers five outstanding clinical advantages:

- 1) Maintains normal or near-normal blood pressure indefinitely;
- 2) Combines additive vasodilation of two of the safest, most effective antihypertensive agents;
- 3) Tranquilizes the emotional patient;
- 4) Avoids unpredictable responses by the use of pure, crystalline alkaloids which are completely standardized by chemical assay;
- 5) Permits dosage schedule to be established easily, with continued and uniform responses to be expected thereafter.

SUPPLIED: Each VERALBA-R tablet contains 0.4 mg. of protoveratrine and 0.08 mg. of reserpine. In bottles of 100 scored, uncoated pink tablets.

PITMAN • MOORE COMPANY

DIVISION OF ALLIED LABORATORIES, INC.

INDIANAPOLIS, INDIANA

*TRADEMARK

Please Mention this Journal when writing to Advertisers

Is there an engineer in the waiting room?



You, as a physician, are thoroughly trained and experienced in detecting the clinical conditions that affect your patients' physical being. They depend on you completely for a knowledge and guidance not possessed by themselves. Conversely, do you not similarly look to professional men in other fields for aid when the need arises?

For example, when there's the question of quality in the consideration of a new piece of diagnostic equipment — such as an electrocardiograph — an engineer can tell better than anyone, sometimes with just a superficial examination, how well the instrument is designed and made. He notices such things as workmanship, the quality of materials, and the grade of the components. As an engineer he would be sure to see the value in unitized construction in the Viso-Cardiette — amplifier, control panel and recorder as three basic assemblies — and the advantages of inkless recording in true rectangular coordinates.

He would remark about the minimum of moving parts, the ruggedness of construction, and the precision instrument quality of the purchased components.

* This EXCLUSIVE plan places a Viso-Cardiette in your hands for 15 days. At the end of that trial period, if you are not completely satisfied with the instrument, you simply return it to us and that is all! You're under NO OBLIGATION.



If you are trying to decide which electrocardiograph to buy, we invite this type of comparison between the Viso-Cardiette and any other instrument. To make such an examination of the Viso possible, you may have a Viso for a 15-day trial* without any obligation whatsoever.



**SANBORN
COMPANY**

Cambridge 39, Massachusetts

Your New Electrocardiograph-- WILL IT HAVE THESE FEATURES?

STABILITY when switching rapidly from one lead to another.

PRECISION RECORDING sensitive to rapid changes in potential.

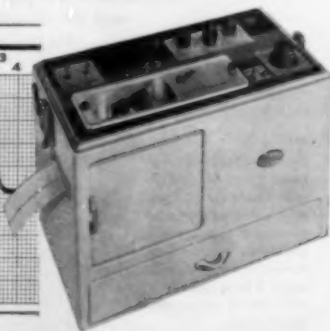
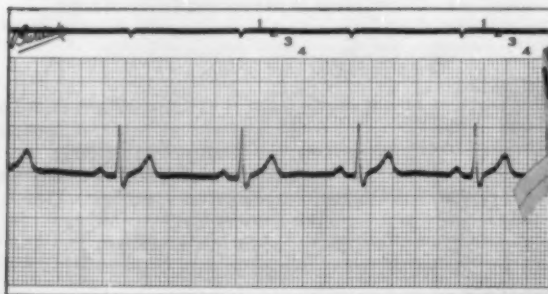
CONTINUOUS TIME MARKER independent of chart; assures accuracy of time factor.

SIMPLIFIED LEAD MARKING; automatic for first four leads.

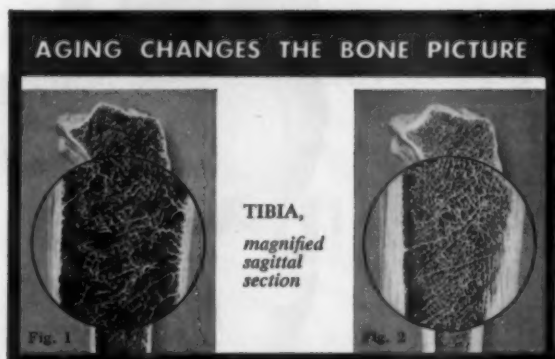
All these features are available in the



**E K - 2
DIRECT-RECORDING
ELECTROCARDIOGRAPH**



THE BURDICK CORPORATION MILTON, WISCONSIN



Estrogen and androgen are vitally concerned with the preparation and recalcification of bone matrix, and this readily explains why declining sex hormone production associated with aging so frequently leads to postmenopausal and senile osteoporosis. Note typical atrophic changes characteristic of postmenopausal osteoporosis (fig. 1), in contrast to normal bone matrix (fig. 2).

Not generally realized is that some degree of osteoporosis is almost "physiologic" after the menopause, and that this bone disorder is present clinically in about 10 per cent of all women over 50 years of age.*

With combined estrogen-androgen therapy, pain in the spine and other bones is markedly relieved in a matter of weeks or months. The prognosis for bone recalcification, following extended periods of treatment, is good.*

Estrogen and androgen as combined in "Premarin" with Methyltestosterone provide a dual approach for maximum efficiency in treating osteoporosis. A brochure outlining full details of therapy is available on request.

*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, Philadelphia, The Blakiston Company, 1950, p. 655.

"Premarin" with Methyltestosterone is supplied in two potencies: the yellow tablet (No. 879) contains 1.25 mg. of conjugated estrogens equine and 10 mg. of methyltestosterone; the red tablet (No. 878) contains 0.625 mg. and 5 mg. respectively. Both potencies are available in bottles of 100 and 1,000 tablets.

"PREMARIN" with METHYLTESTOSTERONE
for combined estrogen-androgen therapy



5424

Ayerst Laboratories • New York, N. Y., Montreal, Canada



*"complete
symptomatic
relief" in
peptic ulcer
patients...*

Antrenyl®

In a recent study, patients with acute symptoms of peptic ulcer obtained relief 24 to 36 hours after taking Antrenyl, a potent anti-ulcer agent.

ANTRENYL—prescribed as an adjunct to rest, sedation, antacids and diet—offers the peptic ulcer patient optimal benefits. It is also of value in other conditions marked by gastrointestinal spasm.

ANTRENYL inhibits gastrointestinal motility and gastric secretion. Side effects are either mild or absent, and there is no bitter aftertaste.

ANTRENYL is available as tablets (white, scored), 5 mg.; syrup, 5 mg. per 4-ml. teaspoonful; tablets (peach-colored, scored), 5 mg. with phenobarbital, 15 mg.; Pediatric Drops (with dropper), each drop containing 1 mg. of Antrenyl bromide.

S. ROSSIO, M.P., AND GRAY, G.L.: AM. J. DIGEST. DIS. 19:100 (JUNE) 1952.

Antrenyl® bromide (oxyphenonium bromide CIBA)

C I B A
SUMMIT, N. J.

2/5000

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when resistance to other
antibiotics develops...

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Current reports^{1,2} describe the increasing incidence of resistance among many pathogenic strains of microorganisms to some of the antibiotics commonly in use. Because this phenomenon is often less marked following administration of CHLOROMYCETIN (chloramphenicol, Parke-Davis), this notably effective, broad spectrum antibiotic is frequently effective where other antibiotics fail.

Coliform bacilli—100 strains

up to 43% resistant to other antibiotics;
2% resistant to CHLOROMYCETIN.¹

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up to 73% resistant to other antibiotics;
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CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

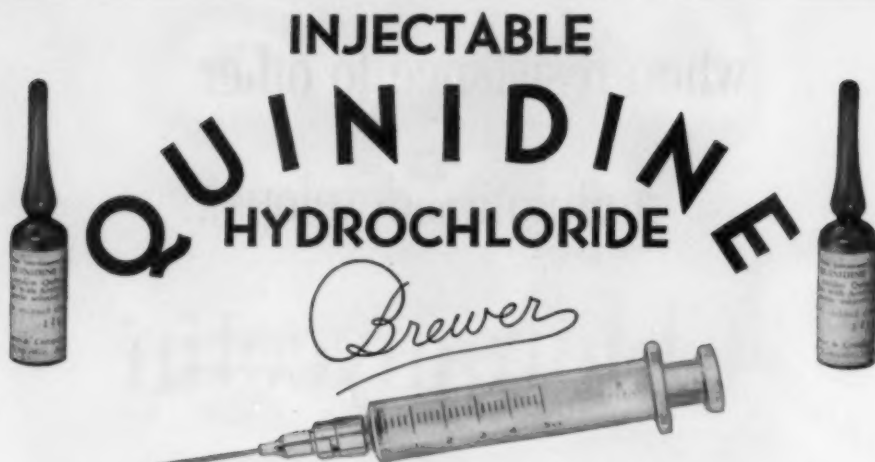
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Administration: INTRAMUSCULARLY or if necessary INTRAVENOUSLY

Available: Quinidine Hydrochloride Injectable (0.6 Gm.) in 5 cc. ampul
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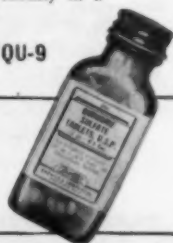
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3. Armbrust, Chas. A. Jr. and Levine, Samuel A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases: Circulation, 1: 28-39 (Jan.) 1950
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2. Schwartz, E.: J. Allergy 25:112-119, March, 1954.

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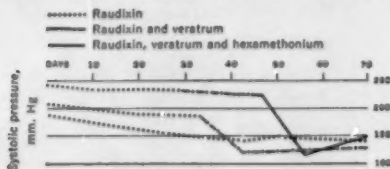
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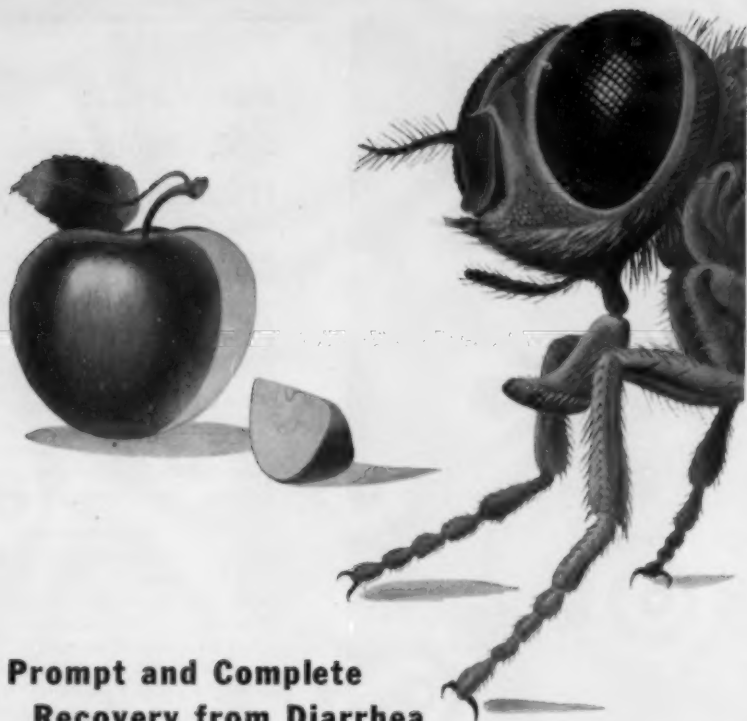
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1. Russ, J. D.: Personal communication

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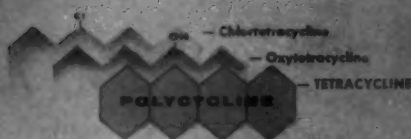
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average adult,
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1. Reifenstein, E. C., Jr., Howard, R. P., Turner, H. H., and Lowrimore, B. S.: J. Am. Ger. Soc. 2:293 (May) 1954. 2. Looney, J. M.: Presented by title at the 36th Annual Meeting of The Endocrine Society, June 17-19, 1954, San Francisco, Calif. 3. Lloyd, C. W.: Personal communication.

C I B A
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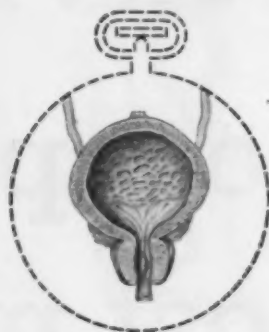
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Aminophylline..... 3 gr.
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REFERENCE: 1. J. Pediat. 42:292 (March) 1953.

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


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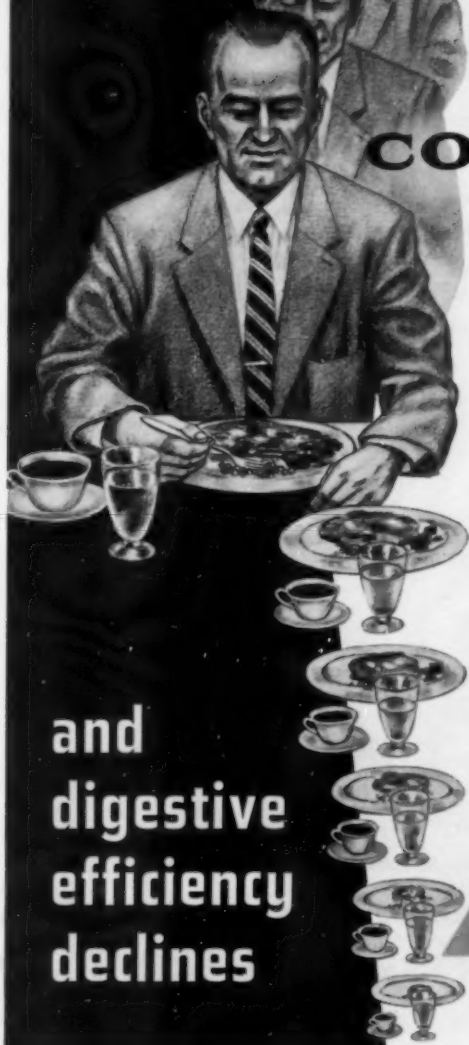
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hydrochloric acid in the stomach, and desoxycholic acid and pancreatin in the small intestine.

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A sugar-coated outer layer designed to release in the stomach:

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References: 1. Lee, R. I.: Chicago M. Soc. Bull.: 48:503, 1946. 2. Golub, M.: Am. J. Digest. Dis. 18:308, 1951. 3. McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, pp. 416, 476.

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"Azopyrine*... has been effective in controlling the disease in approximately two-thirds of patients who had previously failed to respond to standard colitis therapy currently in use."

1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

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Reports on Azulfidine:

(This drug has been presented under three different names, which appear in the literature cited, viz: Salazopyrin, Azopyrin and the now established name in America, Azulfidine.)

1949 "The administration of salicylazosulfapyridine (salazopyrin) produced marked improvement in 8 of 12 cases of ulcerative colitis."

Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

1950 Bargen reports that since 1949 approximately 100 patients have been treated with Azulfidine. "The results have been extremely satisfactory in most cases." Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.

Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.

Morrison, L. M.: Gastroenterology 21:133, 1952.

1953 Morrison publishes results from a series of 47 patients treated with Azulfidine compared to a control series of 60 patients receiving other current therapy: In the Azulfidine-series 18% are symptom-free and 52% improved, compared to 5% and 32% respectively, in the control series.

J. A. M. A.: 151:366 (Jan. 31) 1953.

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For detailed instructions on the materials and techniques required for the use of C·R·P·A — Schieffelin, just send us a request and we will mail you a descriptive brochure.



1. Kroop, I. G. and Shackman, N. H.: *Proc. Soc. Exper. Biol. & Med.* 86:95 (May) 1954.
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3. Scollerman, G. H., et al.: *Am. J. Med.* 15:645 (Nov.) 1953.
4. Hedlund, P.: *Acta med. Scandinav.* Supplement 196:579, 1947.

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Protein.....	14.6 gm.	17.9 gm.	
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Carbohydrate.....	24.7 gm.	28.6 gm.	
Iron.....	1.5 mg.	4.46 mg.	
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Cholesterol.....	.299 mg.	38.4 mg.	
Calories.....	291 mg.	270	

*Nutritive value of Eggnog from Bowes and Church, 7th Ed. 1951.

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Clinicopharmacologic Properties of Gitaligin* [Amorphous Gitalin]

The following table is quoted verbatim from the report by Dimitroff, S.P.; Griffith, G.C.; Thorner, M.C. and Walker, J.: Clinical Evaluation of Gitalin in the Treatment of Congestive Heart Failure, *Annals Int. M.* 39:1189 (Dec.) 1953.

Derivation	<i>Digitalis purpurea.</i>
Appearance	Amorphous white powder.
Uniformity	Constant from batch to batch.
Absorption	Rapid and complete from gastrointestinal tract.
Route of administration	Oral.
Dissipation	Rate of excretion between the rapidly excreted Digoxin and slowly excreted leaf or digitoxin.
Range of toxicity	Less toxic than other glycosides. Digitalizing dose is about 1/3 amount of the toxic dose.
Dosage by rapid method	2.5 mg. first, then 1.0 mg. every 6 hours, or 1.0 mg. every 4-6 hours until toxic or therapeutic effect appears (usually 24-48 hours.)
Dosage by slow method	A single dose of 1.5 mg. daily, or 0.5 mg. t.i.d. until toxic or therapeutic effect appears (usually 4-7 days).
Symptoms of toxicity	Same as for other glycosides, i.e., anorexia, nausea, vomiting, color-vision, ectopic beats, ST-T changes.

WHITE LABORATORIES, INC., Kenilworth, N. J.

Simple dosage equivalent: 0.5 mg. (1 tablet) of Gitaligin is approximately equivalent to 0.1 Gm. (1½ gr.) digitalis leaf. Gitaligin is supplied in 0.5 mg. tablets, deep scored for accuracy and flexibility of dosage—in bottles of 30 and 100.

Gitaligin is accepted by the Council on Pharmacy and Chemistry of the American Medical Association.



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gives ulcer relief

without side effects

Gastric hyperacidity is controlled by Maalox-Rorer without constipation or other side effects commonly encountered with antacids. Relief of pain and epigastric distress is prompt and long-lasting. Available in tablets and liquid form.

Suspension Maalox-Rorer contains the hydroxides of Magnesium and Aluminum in colloidal form. The smooth texture and pleasant flavor make it highly acceptable, even with prolonged use.

Supplied: in 355 cc. (12 fluid ounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension Maalox.)

Samples will be sent promptly on request.

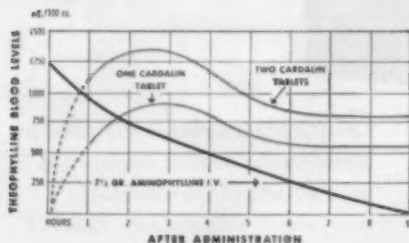
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EVEN MORE EFFECTIVE ORALLY Than Aminophylline Intravenously

Now you can give 5 grains of aminophylline orally with better results and complete safety. Of the oral aminophyllines, only Cardalin produces higher and better sustained blood levels than those attained with the customary intravenous dose of $7\frac{1}{2}$ grains.



(Adapted from Bickerman, H. A., et al.: *Ann. Allergy* 11: 301, 1953, and Truitt, E. B., Jr., et al.: *J. Pharmacol. & Exper. Therap.* 100: 309, 1950.)

Bickerman, et al.¹ found that "the plasma theophylline levels on 300 and 600 mg. of Cardalin (1 and 2 tablets) revealed appreciable concentrations of theophylline in the circulating blood as long as seven hours after administration."

Aminophylline, an excellent drug, had to be made effective and practical orally. One of the principal problems of aminophylline has been that of administration. A small oral dosage of $1\frac{1}{2}$ gr. or even 3 gr. does not produce theophylline blood levels high enough to accomplish the therapeutic objective. Attempts to achieve signifi-

Cardalin

tablets

cant plasma theophylline levels with higher oral dosage failed because of the high incidence of nausea and vomiting.

Irwin-Neisler research teams worked on the formulation of an oral dosage of aminophylline which would be therapeutically effective and well tolerated by the majority of cases under intensive treatment. For the first time, the highest concentration of aminophylline for oral administration is supplied in Cardalin tablets. By the use of two protective factors, Cardalin enables the physician to administer high doses of aminophylline with a comparatively low incidence of gastrointestinal disturbance.

Each Cardalin Tablet contains:

Aminophylline.....5.0 gr.
Aluminum Hydroxide.....2.5 gr.
Ethyl Aminobenzoate.....0.5 gr.

Supplied: Bottles of 50, 100, 500 and 1000.

Also available **Cardalin-Phen** containing $\frac{1}{4}$ gr. phenobarbital per tablet.

1. Bickerman, H. A., et al.: *Ann. Allergy* 11: 301, 1953.

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(2) McHardy, G. and Browne, D.: Soc. Med. J. 45:1139, 1952

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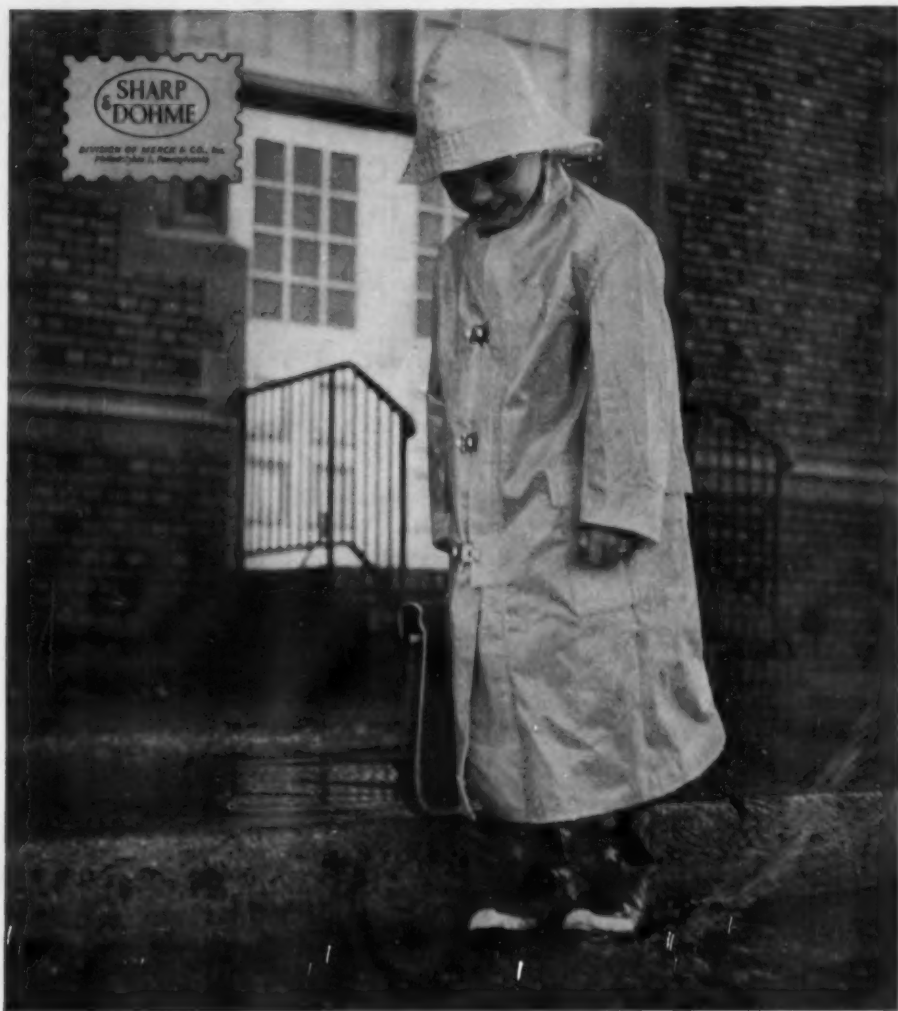
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CERVICAL SPONDYLOSIS *

By SIR RUSSELL BRAIN, F.A.C.P. (Hon.), *London, England*

UNTIL recently very little was known about the importance for neurology of changes in the cervical spine. Yet today we realize that its disorders constitute an important cause of lesions of the spinal cord and nerve roots and lead to much disability which is often severe, particularly in middle age and later. Today I shall confine my attention to cervical spondylosis.

May I begin by reminding you of certain anatomic facts which have an important bearing upon the mode of production of symptoms. The first and second cervical vertebrae differ from the rest in that there is no intervertebral disc between them, and the spinal nerve roots emerge behind a single articulation, whereas below the second cervical vertebra the spinal nerve roots emerge through an intervertebral foramen which lies between two articulations, the uncovertebral joint anteromedially and the joint articulating the pedicles, or apophyseal joint, posterolaterally.

Opposite each foramen the dural sac has a small extension, the dural root pouch, through which each nerve root is conveyed in a smoothly curved course to the point at which it leaves the dural sac. Each nerve root being also enclosed by the arachnoid, the dural root pouch contains an extension of the subarachnoid space. Frykholm has pointed out that the dural root pouches vary even in normal individuals. They may be downwardly, transversely or upwardly directed. Owing to disease, as we shall see, the root pouch may be partially or completely obliterated, with the formation of an acute angle at the upper or lower point at which it joins the main dural sac, or at both.

There are three main sites of intervertebral disc protrusion in the cervical region: (1) dorsomedial, (2) dorsolateral and (3) intraforaminal.

In considering the pathogenesis of cervical intervertebral disc protrusion, it is important to note that there are two types which are etiologically

* Presented at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 7, 1954.

distinct, even though in their later stages it may be very difficult to tell them apart either pathologically or radiologically. These are (1) nuclear herniation, and (2) annular protrusion. A nuclear herniation may occur either spontaneously or as a result of trauma. Acute nuclear herniation is, in the majority of cases, unrelated to cervical spondylosis and therefore will not be further considered now; but a slight degree of nuclear herniation with some rupture of the annulus fibrosis may be a predisposing cause to the kind of disc degeneration which eventually leads to annular protrusion.

ETIOLOGY AND PATHOLOGY OF CERVICAL SPONDYLOSIS

As the name implies, cervical spondylosis is a degenerative disorder which is unrelated to inflammation and infection. The changes may involve the articulation between only one pair of vertebrae or the lesions may be multiple, in which case the joints affected may be those of adjacent vertebrae or remote from one another. Moreover, the lesion may be limited to the cervical spine, or may be generalized throughout the whole spine, and a combination of cervical and lumbar spondylosis is quite common.

The main factor in the causation of cervical disc degeneration is undoubtedly age, and a large majority of patients are over the age of 50. It has been shown that age leads to a gradual dehydration of the discs, which thus lose some of their elasticity. The result of this is to throw additional wear and tear upon the bodies of the adjacent vertebrae, which respond by increased bone formation from their margins, which fuses with the cartilage of the protruding degenerating disc. The result is the characteristic osteophytes which project into the spinal canal at one of the sites already mentioned or into the intervertebral foramen. The bone changes are thus secondary to the disc degeneration.

It is probable that the great mobility of the cervical spine contributes to the wear and tear upon the discs, and it is noteworthy that a congenital abnormality adds to the strain upon neighboring discs. This explains why congenital fusion of two or more cervical vertebrae is encountered more frequently among patients suffering from cervical spondylosis than in a group of controls.

In my own series¹ previous trauma was thought to have been a contributory factor in 20 to 30 per cent of cases, but this figure may be too low, as it is easy for patients to forget head injuries which may have occurred many years before but which, nevertheless, initiated a slow process of disc degeneration.

It has sometimes been stated that cervical spondylosis occurs most frequently in the lower part of the cervical spine. In our series, however, it occurred with about equal frequency in all intervertebral discs in the neck from the second cervical vertebra downwards, except that the disc between the seventh cervical vertebra and the first dorsal was rarely affected. The disorder was limited to a single disc in one third of our cases.

Although disc degeneration usually limits movement between the two vertebrae separated by the degenerating disc, exceptionally there is abnormal mobility at this site, in which case the body of the higher vertebra may move either forwards on flexion of the neck or backwards on extension. This abnormal mobility adds considerably to the effects of cervical spondylosis upon the spinal cord.

THE EFFECTS OF CERVICAL SPONDYLOSIS UPON THE NERVOUS SYSTEM

Cervical spondylosis may cause damage to the spinal nerve roots (or radicular nerves) or the spinal cord or both. A dorsolateral protrusion may compress the nerve roots against the corresponding lamina within the spinal theca, while an intraforaminal protrusion may compress them within the foramen. Several factors, however, contribute to this. The narrowing of the intervertebral disc itself narrows the foramen by bringing the upper and lower edges closer together. Disc degeneration leads to osteophytes extending into the foramen from the uncovertebral joints, while the narrowing of the foramen throws an increased strain upon the posterior articulations and tends to produce osteophytes in them. The result of these processes is an obliteration of the root sleeve by fibrous tissue—Frykholm's root sleeve fibrosis—and this in turn interferes with the blood supply of the roots.

Frykholm² has made the important observation that the pathologic change of root sleeve fibrosis is not necessarily limited to the roots passing through foramina which exhibit bony narrowing. He points out that narrowing of the cervical intervertebral discs shortens the cervical spine relative to the spinal cord and therefore tends to displace the nerve roots caudally in the foramina. As a result, they may be subjected to pressure by the edge of an intervertebral foramen which is not itself narrowed by osteophytes. Trauma may also occasionally by itself cause root sleeve fibrosis.

The effect of cervical spondylosis upon the spinal cord is even more complex. The most obvious factor is direct compression by the osteophytic protrusions, which act as extradural tumors. The effect of this compression is increased by the fact that the nerve roots, as just explained, are tethered within the foramina and the cord is also restricted in movement by the ligamenta denticulata. Several authors have stressed the importance of vascular factors, especially compression of the anterior spinal artery by dorsomedial disc protrusion. The anterior spinal veins may also be compressed, and the narrowing of the intervertebral foramina and root sleeve fibrosis may to some extent interfere with the supply of blood which normally reaches the spinal cord through the radicular arteries. It is possible, also, that cervical spondylosis may diminish the blood flow through the vertebral arteries. Finally, in patients of an age at which cervical spondylosis is most commonly encountered, degenerative changes in the blood vessels may also be an important contributory factor. If the vessels are atheromatous, ischemia is much more readily produced than if they are normal.

Movements of the neck are also important. Even normal movements may introduce a repeated traumatic factor when the cervical cord is already compressed by a disc protrusion. As already mentioned, this is even more severe when the disc degeneration causes abnormal mobility of some intervertebral joints. Finally, a traumatic movement, especially forcible extension of the neck resulting from a blow on the forehead, may, in the presence of cervical spondylosis, produce severe and lasting damage to the spinal cord or nerve roots, even without producing any bony damage or leading to rupture of ligaments or increase in the degree of disc protrusion.

The effect of these various factors is to produce in milder cases patches of demyelination with ascending and descending degeneration, while in more severe cases, or after severe trauma, the result is an extensive necrosis of the cervical cord in which it may be difficult, or impossible, to distinguish the gray matter from the white. The pathologic changes are best described as a myelopathy or, in severe cases, a myelomalacia.

RADICULAR SYMPTOMS

It is perhaps worth while to draw attention in passing to the widespread distribution of sensory symptoms, particularly pain, which may occur as the result of irritation of a single posterior root on account of the fact that the sensory supply to muscles, bones and joints, i.e., the myotome and sclerotome, extends far beyond the cutaneous supply or dermatome. For example, the pain produced by irritation of the sixth or seventh cervical posterior root commonly spreads not only down the whole of the upper limb to the thumb and index finger and the middle finger, respectively, but also to the back of the neck and to the back and front of the chest. This explains why an acute compression of either of these nerve roots may closely simulate the pain of cardiac disease.

It is noteworthy that there often seems to be no precise relationship between the chronicity of the cervical spondylosis and the acuteness of the radicular symptoms. One would naturally expect chronic narrowing of the intervertebral foramen to be associated with chronic symptoms of root irritation; but, on the one hand, a foramen may be narrowed without apparently producing any sensory symptoms whatever, while, at the other extreme, bony changes which are obviously of very long standing may be associated with pain of quite acute onset.

I shall not recapitulate the ordinary symptoms of so-called brachial neuritis resulting from cervical spondylosis, for they are familiar enough. But I shall confine myself to symptoms of special interest.

Acroparesthesia may be defined as an unpleasant and painful tingling sensation occurring in one or both hands, usually in middle aged women and chiefly at night, tending to awaken the patient in the early morning and to pass off an hour or so after she has got up. It is unlikely that this symptom, which is essentially that of irritation of sensory fibers, is produced by a

lesion in only one situation, and I believe that acroparesthesias, as above defined, may be the result either of cervical spondylosis or of a costoclavicular syndrome, or of compression of a median nerve in the carpal tunnel. I shall not stop now to differentiate these, but merely remark that acroparesthesias are sufficiently often a symptom of cervical spondylosis to make it desirable in all such cases to x-ray the cervical spine.

In most cases of cervical spondylosis in which the nervous lesion is limited to the spinal roots, muscular wasting and weakness are not conspicuous. Exceptionally, however, these symptoms may be severe and associated with fasciculation and occur in the absence of objective sensory changes. The muscular wasting, in fact, may be sufficiently severe to suggest the diagnosis of progressive muscular atrophy. Frykholm explains this as due to the fact that, since the anterior root tends to lie caudally to the posterior root, it may easily be compressed against the lower lip of the intervertebral foramen if there is a caudal shift in the position of the roots within the foramina or if osteophytes narrow the foramina from below.

Periarticular adhesions around the shoulder joint, the "frozen shoulder," causing severe restriction of movement accompanied by pain, may be due to any cause which leads to either prolonged immobility of the joint or reflex muscular spasm around it. It is worth noting that cervical spondylosis is one such cause, probably operating in both ways.

SPINAL CORD SYMPTOMS

The history of patients who complain of symptoms resulting from damage to the spinal cord by cervical spondylosis is usually one of many months' duration, and sometimes extends over a period of years, and the onset is insidious unless, as occasionally happens, it is accelerated by trauma. The chief initial symptoms are progressive weakness of the lower limbs, numbness and clumsiness of the hands, pain of radicular distribution extending over one or both upper limbs or sometimes irradiating to the chest, and cramp or a sensation of numbness in the lower limbs. Sphincter involvement is rare, except in the very late stages, and symptoms referred to the neck itself are usually slight and inconspicuous, though most patients if questioned will admit that from time to time they have suffered from pain in the neck.

The clinical picture is extremely variable, which is easy to understand in the light of what has been said about the pathology. The cord may be damaged at a single level, or at several levels, and the level affected may be above the cervical enlargement or at any of the segments within the cervical enlargement, or a combination of these may occur. Furthermore, the damage to the cord itself may be patchy and comparatively slight, or fairly diffuse and much more severe, and it may or may not be complicated by damage to the spinal roots.

In the upper limbs muscular wasting is usually slight, except that it is

quite common to find fairly severe wasting of the small muscles of the hands even with a lesion above the eighth cervical and first dorsal segments. Weakness of the upper limbs is common, but is more often due to an upper motor neurone lesion than to a lower motor neurone lesion, though both may be present. In the former case the tendon jerks in the upper limbs are usually all exaggerated, but it is common to find an inverted radial reflex with an increased triceps jerk and flexor finger jerk, although sometimes the triceps jerks are diminished. In the lower limbs the motor picture is one of spastic weakness with exaggerated knee and ankle jerks and bilateral extensor plantar reflexes. In the upper limbs it is common to find cutaneous sensibility diminished over the periphery, and this is sometimes accompanied by severe loss of postural sensibility in the digits. Analgesia and thermoanesthesia may be present over the lower limbs as the result of damage to the spinothalamic tracts, and again severe postural loss is sometimes found in the toes. In the neck there is often an exaggerated lordosis, especially common in women, and some limitation of active and passive movement which may be accompanied by crepitus and slight pain are often encountered.

In the majority of cases the cerebrospinal fluid is normal in dynamics and composition. Occasionally both are compatible with obstruction of the spinal subarachnoid space.

RADIOGRAPHY

In the routine radiography of the cervical spine in suspected cases of cervical spondylosis we find it necessary to take three lateral views in the erect, flexed and extended postures in order to show abnormal mobility. In addition, we take an anteroposterior view, and right and left oblique views to show the intervertebral foramina. Attention is paid to the thickness of the discs themselves, to the presence of osteophytes either anteriorly or posteriorly in the lateral views, or in relation to the neurocentral joints in the anteroposterior view, or the intervertebral foramina in the oblique view. Myelography is often necessary when there is damage to the spinal cord, since it may be impossible to decide from the lateral plain x-rays how large the posterior osteophytes are. Myelography may also be useful to show in the anteroposterior view defective filling of the root sleeves.

A comparison of the radiologic, operative and pathologic findings leads me to stress four general conclusions: 1. Radiographic evidence of a narrowed intervertebral disc is not evidence of a disc protrusion. 2. Similarly, radiographic evidence of a narrowed intervertebral foramen is not evidence of compression of the corresponding nerve roots. 3. The presence of an intervertebral foramen which is normal radiographically is not evidence that the corresponding nerve roots are also normal since, as mentioned above, they may be the site of root sleeve fibrosis even though the surrounding bones appear normal on the x-rays. 4. Finally, it must always be re-

membered that cervical spondylosis is not necessarily the cause of associated symptoms of nervous disease, even when these are evidence of a lesion of the spinal cord in the cervical region.

DIAGNOSIS

Because of the great variability of its clinical features, cervical spondylosis may closely simulate a number of other disorders. When it produces muscular wasting and fasciculation in the upper limbs, accompanied by spastic weakness of the lower limbs, it may be difficult to distinguish from amyotrophic lateral sclerosis. Ataxic weakness of the upper limbs, with spastic weakness of the lower limbs and some degree of superficial or deep sensory loss, may suggest disseminated sclerosis. The combination of the symptoms of pyramidal and posterior column lesions in the upper and lower limbs, perhaps accompanied by cutaneous anesthesia of glove distribution, may lead to a mistaken diagnosis of subacute combined degeneration. The sole symptom of cervical spondylosis may be spastic weakness of the lower limbs, and this may be thought to indicate a lesion of the spinal cord at the dorsal level, or the condition may be labeled primary lateral sclerosis. Rather surprisingly, perhaps, syringomyelia is not often simulated with any exactitude, but the symptoms may suggest either an intramedullary tumor of the spinal cord or an extramedullary tumor. If, however, the possibility of cervical spondylosis is borne in mind, the diagnosis can usually be settled beyond doubt by radiography of the cervical spine, followed, if necessary, by myelography.

PROGNOSIS AND TREATMENT

Before discussing treatment it is necessary to consider the natural course of the disease when untreated. In most cases in which the spinal cord is involved the lesion tends to progress slowly for a period of several years and then to remain stationary, leaving the patient still able to get about, though considerably disabled. Only exceptionally does progressive deterioration occur until the patient is bedridden. In a sense, therefore, time is on the side of treatment, and if by treatment the patient's deterioration can be arrested, and better still if his condition can be improved, there is hope that he may be stabilized indefinitely.

From what has been said it will be clear that immobilization of the neck is the measure most likely to bring about arrest of the pathologic changes in the spinal cord, and it is our practice to begin with a plaster collar and after a few weeks to substitute a plastic one, which must be worn for several months. I have not personally been impressed with the value of traction on the head in chronic cervical spondylosis, and I believe that manipulation is a dangerous mode of treatment. The most difficult question to decide is when surgery is indicated. Our experience has, on the whole, tended to make us more conservative than we were at first. Several factors have to

be taken into consideration, namely, the age of the patient, the length of the history, whether the disc protrusion is single or multiple and, finally, the condition of the cardiovascular system. In general, surgery is most likely to be successful when the patient is relatively young, when the history is relatively short, when the disc protrusion is single rather than multiple, and when the cardiovascular system is normal. Conversely, we have found that contraindications to surgery are when the patient is old, when the history is a long one, when the lesions are multiple and when there is evidence of generalized atheroma with or without hypertension. My surgical colleague, Mr. Douglas Northfield, favors decompression rather than an attempt to remove an anteriorly placed osteophyte. In certain circumstances it may be helpful to decompress the nerve roots within the foramina, and when there is abnormal mobility of the intervertebral joints fusion may be called for.

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CHEMOTHERAPY OF LEUKEMIA, HODGKIN'S DISEASE AND RELATED DISORDERS *

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THE object of this report is to discuss the chemotherapy of leukemia, Hodgkin's disease and the related disorders in the light of our own experience since the development of interest in this field 10 years ago.^{1,2} A large number of chemotherapeutic agents has been discovered since that time but only a few have earned a solid position in the list of useful drugs.

The available chemotherapeutic agents can be best classified and discussed in relation to four groups of disorders, since different ones have been found to be particularly effective in each group. The four groups are as follows:

1. *Hodgkin's Disease.* Here, in decreasing order of effectiveness and value, mention may be made of methyl-bis(β -chloroethyl) amine hydrochloride or nitrogen mustard, triethylene melamine (TEM),³ triethylene phosphoramide (TEPA) and diethylene phosphoramide (DEPA),⁴ and β -naphthyl-di-2-chloroethylamine (R48).⁵ Only the first two will be considered.

2. *Chronic Lymphocytic Leukemia, Lymphosarcoma and Reticulum Cell Sarcoma.* Here TEM is particularly important.

3. *Chronic Myelocytic Leukemia.* For the treatment of this disease, "Myleran" (1,4-dimethanesulphonoxybutane),⁶ urethane (ethyl carbamate)⁷ and a colchicine derivative, Demecolcin,⁸ deserve attention.

4. *Acute Leukemia.* The useful agents are the anti-folic acid compounds,⁹ the hormones, ACTH and cortisone,¹⁰ and the purine antagonist, 6-mercaptopurine.¹¹

HODGKIN'S DISEASE

A 10 year experience¹² has established clearly the value of nitrogen mustard in the chemotherapy of Hodgkin's disease. It is difficult to prove that life has been significantly prolonged by the use of nitrogen mustard, or even by alternating nitrogen mustard with radiation therapy as compared with radiation therapy alone, for the course of this disease is variable and ranges from that of the acute fulminating form to the much slower

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type marked by long remissions. However, there can be no question that patients have been maintained in an asymptomatic state for a greater proportion of their disease course than had been achieved with radiation therapy alone, the amount of time spent undergoing therapy and hospitalization has been shorter, and the total economic burden has been distinctly lower.^{13, 14}

The intravenous administration of nitrogen mustard is followed as a rule, although in varying degree, by prompt relief of the systemic manifestations of the disease. The fever disappears, within a week a sense of well-

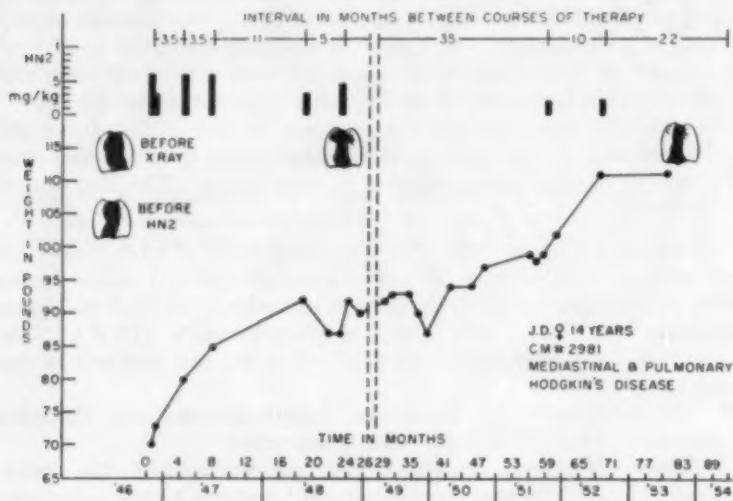


FIG. 1. Course of a 14 year old girl (J. D.) with extensive mediastinal and pulmonary Hodgkin's disease whose illness began 11 months before she was treated with nitrogen mustard as shown in the diagram. Four months before mustard therapy was instituted she received roentgen therapy (1600 r to the anterior and posterior mediastinum) with good results but, one month before, 2000 r produced no improvement. When first treated with nitrogen mustard she was dyspneic and cyanotic and had cough, dysphagia and anorexia. There was an infiltrate in the right middle lung field and in the left lung in the hilar region. The mediastinum was also shifted because of atelectasis of the right lower lobe. After three courses of mustard therapy she improved greatly and since has enjoyed long remissions.

being begins to appear, the size of the enlarged lymph nodes and other tissues decreases, there is gain in weight, and other manifestations of improvement develop. Anemia may decrease or even subside completely. Only in truly terminal cases does this effect not occur. The duration of the remission varies greatly, however, and in our cases has ranged from only several weeks to even several years. Benefit may sometimes be more apparent following a second course of mustard therapy than after the first and, in general, remissions following chemotherapy do not necessarily grow shorter and shorter; they vary in length from one time to another (figure 1).

It is generally agreed that nitrogen mustard therapy is indicated in those cases of Hodgkin's disease in which the disease is widespread and signs of systemic intoxication such as fever, malaise and weight loss are present, as well as in cases which are no longer responsive to radiation therapy. A beneficial effect has been observed many times in patients "resistant" to radiation. Leukopenia in a previously untreated patient is not necessarily a contraindication to its use.

The wisdom of using nitrogen mustard in early cases of Hodgkin's disease is a matter of opinion. It is not clear whether Hodgkin's disease is multicentric in origin rather than a metastasizing disorder which arises from a primary focus. Our practice, even in early cases, is to use nitrogen mustard, in addition to irradiation locally over the obvious site of the dis-

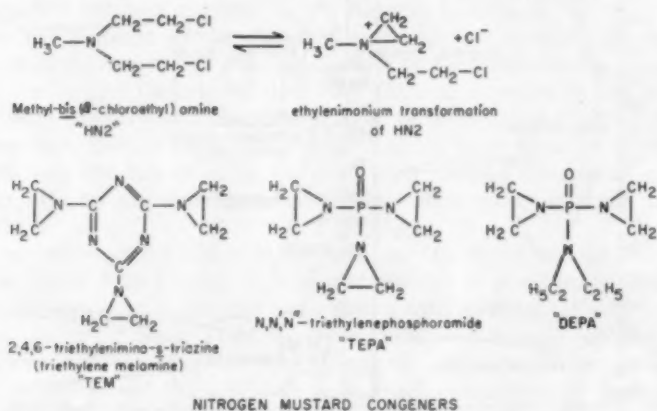


FIG. 2. Nitrogen mustard, TEM and other congeners.

ease; in fact, where the disease is very early and is localized in one area from which surgical removal is technically feasible, we would advise surgery followed by local radiation and then by nitrogen mustard therapy. Unfortunately, the opportunity for such a concerted attack on the disease rarely presents itself. In cases in which the disease is widespread it is our practice to follow mustard therapy by local radiation if there are nodes in the periphery or in the mediastinum which seem resistant to dissolution by intravenous therapy.

The use of heavy barbiturate sedation and, more recently, Chlorpromazine¹⁵ makes it possible to reduce the occurrence and severity of the nausea and vomiting which so often follow the administration of nitrogen mustard. It is our practice to give 0.2 mg. nitrogen mustard per kilogram body weight in a single dose, to be followed on the next day by 0.2 to 0.4 mg./Kg., depending on the total dose previously elected.

Rarely do we use more than a total of 0.6 mg. nitrogen mustard per kilogram body weight in a single course. The drug is usually given in the evening. Currently we prescribe 25 mg. Chlorpromazine at four hour intervals, beginning about noon of the same day. Nembutal (0.1 gm.) is also given at the time of mustard therapy (8 p.m.), the barbiturate and the Chlorpromazine being repeated at midnight if the patient is not already sleeping. If there is need for any additional medication, Chlorpromazine may be given parenterally.

It is clear that therapeutic doses of nitrogen mustard cause destruction of lymphoid tissue and depression of bone marrow function. Mitotic

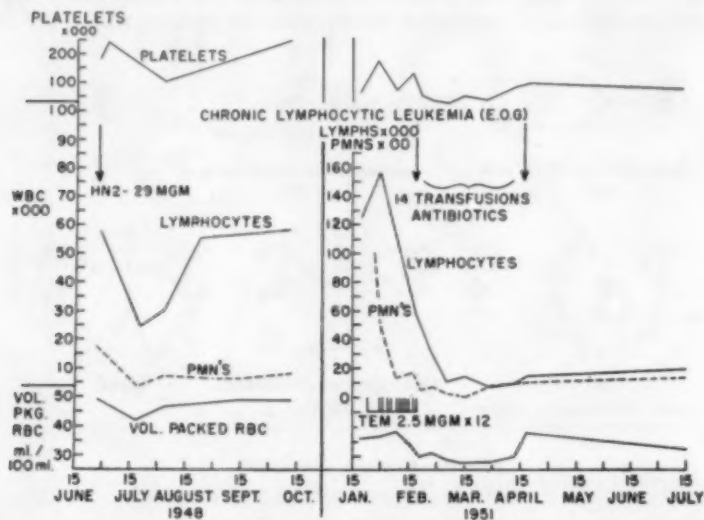


FIG. 3. To illustrate the hidden danger of continuous administration of TEM. This patient with chronic lymphocytic leukemia (E. O. G.) was given 12 doses of 2.5 mg. each over a period of 26 days. A profound leukopenia developed, as well as marked marrow hypoplasia, from which he recovered only after much difficulty. Earlier in his course this patient had done relatively well on nitrogen mustard therapy.

inhibition and alteration of chromosomal structures occur.¹⁶ Possibly an irreversible reaction with nucleotide bases takes place. Although the observable clinical effects are similar, the primary basic reactions initiated by radiation and by nitrogen mustard may be fundamentally different.¹⁷

Serious consequences from the damaging effect of nitrogen mustard on the hemopoietic system can be prevented usually by avoiding the administration of courses of this agent any more frequently than once in six weeks or any sooner than this following radiation therapy. Generally the beneficial effect lasts a good deal longer than this, and there is therefore no need to run the risk which repeated administration at short intervals entails.

Several hundred chemical congeners of nitrogen mustard (figure 2) have been prepared but, with one exception, none has earned a place in the therapeutic armamentarium. There appears to be no advantage in the use of TEPA or DEPA,⁴ the ethylenimine phosphoramides, or R48.⁵ Triethylenemelamine (TEM) (2,4,6-triethylenimino-*s*-triazine),⁶ on the other hand, does have the advantage that it can be given orally and its administration is associated with much less gastrointestinal discomfort than is nitrogen mustard. However, the action of TEM in Hodgkin's disease is slower than that of nitrogen mustard and for this reason we prefer to give the latter to patients with toxic symptoms. TEM does have value for maintenance therapy, since it can be given orally and there is no need for sedation and hospitalization. However, like nitrogen mustard, it is a potent hemopoietic depressant, and multiple doses have a cumulative action which usually first becomes manifest in the form of leukopenia; in short order, severe pancytopenia as the result of bone marrow aplasia may develop. Because of the danger of a cumulative effect on the bone marrow (figure 3), we prefer to give the selected dose of TEM over a period of one to three days, with intervals of a month or longer between courses, rather than at semi-weekly, weekly or biweekly intervals, as some have recommended. In this way the full effect of the dose given can be determined and the danger of a serious and sometimes irreversible cumulative action may be avoided.

The oral dose of TEM is in the range of 0.05 to 0.4 mg. per kilogram; that is, about 5 to 25 mg. in a single course. It is probably unwise to exceed 25 mg. As a rule, not more than a total of 5 mg. should be given on any one day. Since TEM is very reactive with organic molecules it is best given with water on an empty stomach. More consistent absorption probably is achieved if the acid of the stomach is modified by the administration of 2 gm. of sodium bicarbonate at the same time. The agent can also be given intravenously in a dose of 0.05 to 0.15 mg. per kilogram body weight in a course,¹⁸ that is, about one fourth or one half of the dose of nitrogen mustard. Tolerance may decrease as the drug is used, so that repeated courses need to be given with greater and greater caution.

CHRONIC LYMPHOCYTIC LEUKEMIA AND LYMPHOSARCOMA

Some patients with chronic lymphocytic leukemia are particularly sensitive to TEM, and such individuals can be maintained in good condition for long periods of time with the aid of this agent (figure 4). As little as 2.5 mg. by mouth may suffice to produce a significant reduction in the leukocyte count and some reduction in lymphadenopathy. Larger doses should be employed only after the sensitivity of the patient has been evaluated. If lymphadenopathy continues to be troublesome in spite of the use of this agent in small or moderate doses, we prefer to resort to

radiation applied locally rather than to risk severe hemopoietic depression as the result of further increases in the dose.

In this disease some would question the need or even the desirability of therapy as long as no anemia is present and tumor masses are not so large as to be troublesome. Our own attitude is to treat but to err on the side of too little rather than too much. A number of patients, managed in this way, feel better and gain weight.

In general, the treatment of patients with chronic lymphocytic leukemia who have no anemia is not difficult. When anemia develops, however, the problem is more troublesome. We have not found any of the chemo-

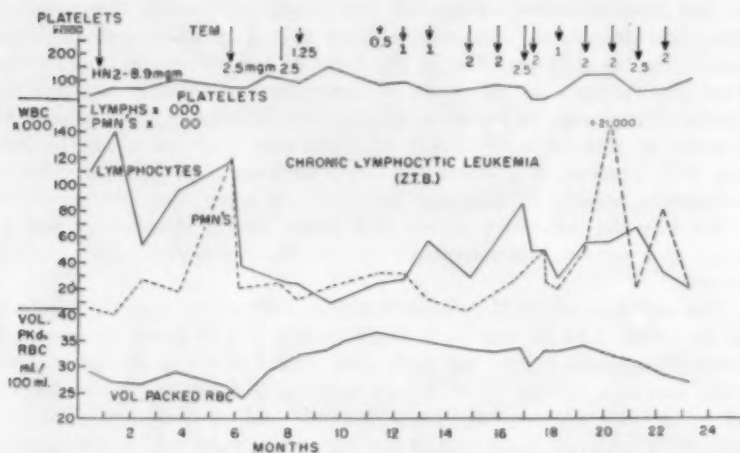


FIG. 4. To illustrate the sensitivity of some patients with chronic lymphocytic leukemia to TEM. In this case (Z. T. B.) 2.5 mg. had a pronounced effect. It should be noted that absolute numbers of lymphocytes and of polymorphonuclear leukocytes are plotted rather than the total leukocyte count.

therapeutic agents which have received extensive trial so far to be of any significant value in this regard. Frequently, however, the patients are able to tolerate the anemia well since it is slow in development. Consequently, it is our practice to use blood transfusions only infrequently. The treatment of hemolytic anemia complicating chronic lymphocytic leukemia will be considered shortly.

The effects of TEM in lymphosarcoma differ widely. As in chronic lymphocytic leukemia, small doses may produce clinical improvement. In many instances TEM has been of little or no value, and in some cases serious hemopoietic depression has developed. Likewise, little can be expected in reticulum cell sarcoma. In this disorder nitrogen mustard has proved of value in some cases but such benefit is usually only temporary.

THE TREATMENT OF HEMOLYTIC ANEMIA COMPLICATING HODGKIN'S DISEASE AND CHRONIC LYMPHOCYTIC LEUKEMIA

In Hodgkin's disease appropriate treatment with nitrogen mustard or roentgen therapy is often effective in relieving the anemia as well as other manifestations of the disorder. When the anemia has been frankly hemolytic, we have found cortisone to be more useful than nitrogen mustard in the treatment of the anemia.

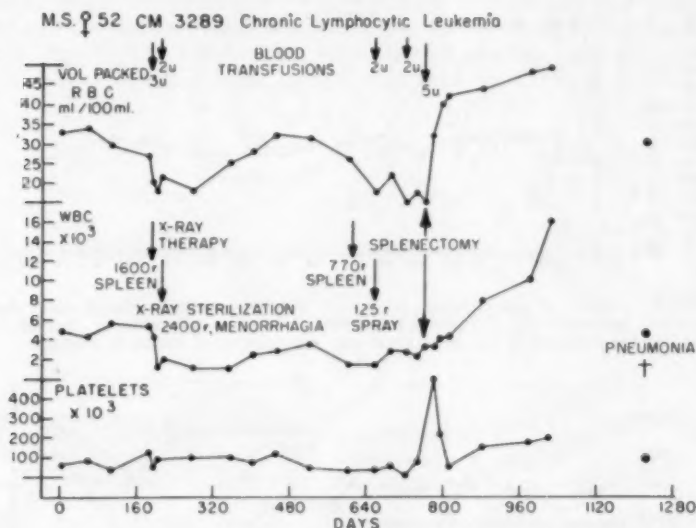


FIG. 5. Dramatic relief of severe anemia and serious thrombocytopenia in a case of chronic lymphocytic leukemia (M. S.) following splenectomy. Sterilization by irradiation of the ovaries had been carried out previously in an attempt to relieve the effect of severe menorrhagia on the anemia. Following splenectomy the patient did very well but succumbed ultimately to pneumonia before she could receive appropriate therapy.

Anemia in chronic lymphocytic leukemia is often an indication that the disease is progressing to the more serious, pre-terminal state. Its treatment has been most difficult. Although classic signs of hemolytic anemia have sometimes been lacking, we have observed relief of the anemia as well as disappearance of the accompanying thrombocytopenia and purpura following splenectomy (figure 5). Such treatment, however, has not always been successful and more recently cortisone has been used instead. Two patients (figures 6 and 7) so treated have now enjoyed remissions from anemia for 10 and six months, respectively, since cortisone therapy was stopped.

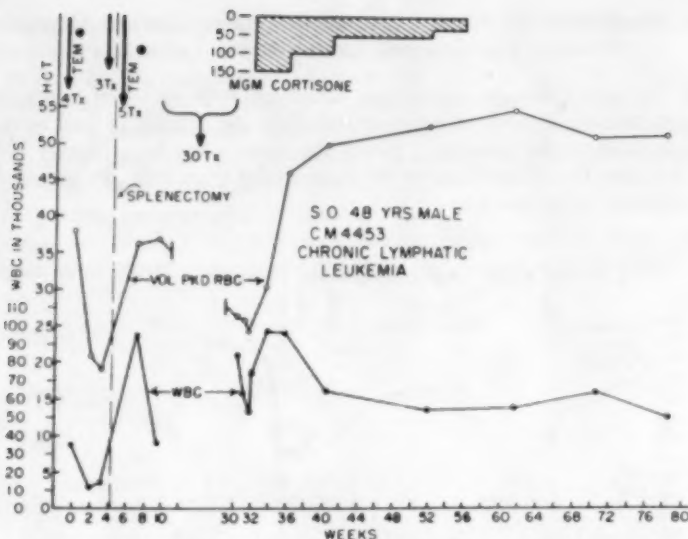


FIG. 6. Failure of splenectomy to relieve hemolytic anemia complicating chronic lymphocytic leukemia (S. O.) compared with effectiveness of cortisone therapy. The anemia has not returned in the 10 months since interruption of cortisone therapy.

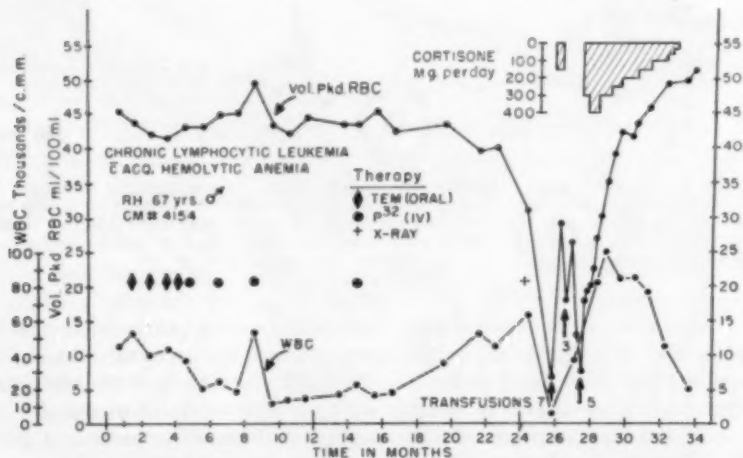


FIG. 7. Course of a patient (R. H.) with chronic lymphocytic leukemia who developed severe anemia. There were slight bilirubinemia (1.5 mg.), spherocytosis, and moderately increased urinary and stool pigments (450 mg. FU day), as well as a 1 plus positive direct Coombs' test. Cortisone therapy was strikingly effective in relieving the anemia. The anemia has not returned in a 6 month period without cortisone. The increase in leukocytosis associated with cortisone therapy was due to a proportionate increase in lymphocytes and granulocytes.

CHRONIC MYELOCYTIC LEUKEMIA

In our experience to date, Myleran, a sulfonic acid ester⁸ (figure 8), has proved to be the most effective and most useful of the chemotherapeutic agents which can be employed in the treatment of this disease. Our observations confirm the report of the English investigators.¹⁹ In oral doses of 2 to 8 mg. daily, usually 4 to 6 mg., the drug has caused a sharp fall in the leukocyte count, usually well pronounced after three weeks of therapy, which is associated with the development of a sense of well being and is followed by relief of anemia, a return to normal in the differential leukocyte count and the platelet count, decrease in the size of the spleen and gain in weight (figure 9). The duration of the remission which occurred in every one of our 11 treated cases ranged from two to 12 months following

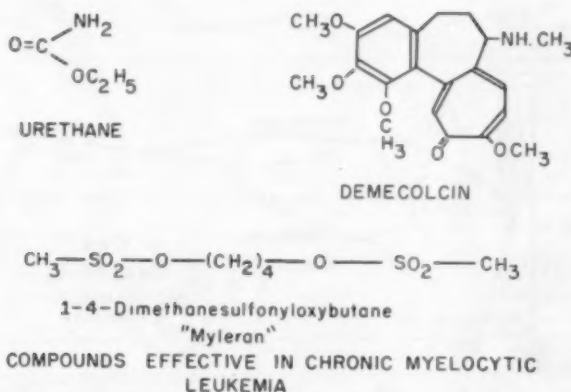


FIG. 8. Chemical structures of Myleran, urethane and Demecolcin.

cessation of therapy. As many as four repeated courses of treatment have been effective, except in one patient in whom anemia failed to be relieved in the fourth course. Galton¹⁹ has observed remissions as long as 21 months in duration. Thrombocytopenia and marrow hypoplasia have been reported following excessive dosage. We have observed bone marrow hypoplasia in only one patient. This patient received 476 mg. of Myleran in a three month period.

The ease with which Myleran can be given and its inexpensiveness make this the therapy of choice in this disease. These are important points in the comparison with roentgen-ray therapy. Further experience is necessary to determine how soon and how often resistance to this agent will develop and, in such cases, whether roentgen therapy or other chemotherapeutic agents will then be effective. It has been observed already¹⁹ that some patients treated by other methods, including roentgen therapy, to

which they were becoming more or less refractory, have responded to Myleran.

Urethane,⁷ which is given in doses of 1 to 4 gm. per day by mouth, has been less consistently useful in the treatment of chronic myelocytic leukemia than Myleran, and its use may be accompanied by vague gastrointestinal discomfort and nausea or sometimes even vomiting. Anemia is less often relieved and splenomegaly may not decrease as much. Urethane is a hemopoietic depressant and protracted administration may result in marrow hypoplasia. Hepatocellular damage has been reported.²⁰

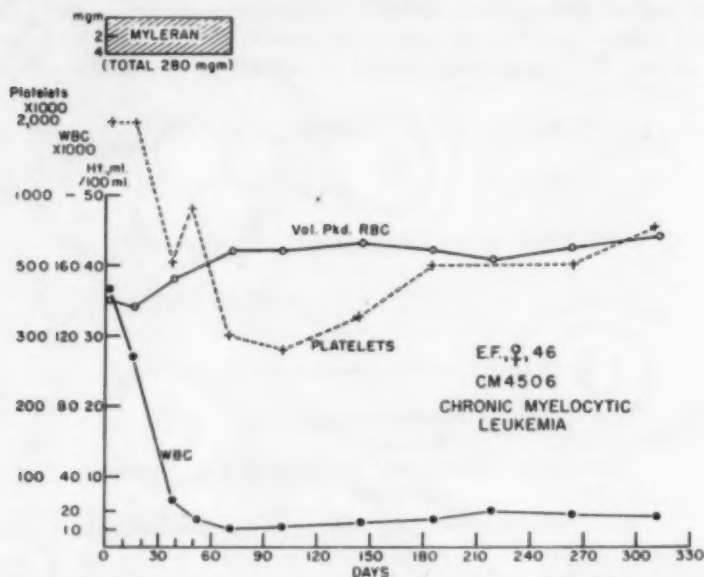


Fig. 9. Effect of Myleran therapy in a case of chronic myelocytic leukemia (E. F.).

A colchicine derivative, Demecolcin, has been reported⁸ to have only one thirtieth the toxicity of colchicine, together with a marked specific effect on granulocytes. Thus this may prove to be another orally effective agent for the treatment of chronic myelocytic leukemia. A beneficial effect in the "acute" terminal phase of this disease has also been reported.

ACUTE LEUKEMIA

In a disease like acute leukemia, where such varied factors as the age of the victim, early diagnosis, the occurrence of severe hemorrhages or infections and the availability of supportive measures may all influence the outcome, the evaluation of chemotherapeutic agents is most difficult. In

this disease, in contrast to what is observed in most other disorders, the development of a complicating acute infection may be associated with a temporary remission rather than relapse.²¹ Again, remissions have been observed following blood transfusions and, for a time, exchange blood transfusion was in vogue as a form of therapy. Nevertheless, it seems clear that, since the 1920's, there has been a steady increase in the survival time of the child patient with leukemia.²² This probably is the consequence of the use of blood transfusions, sulfonamides and penicillin and, more

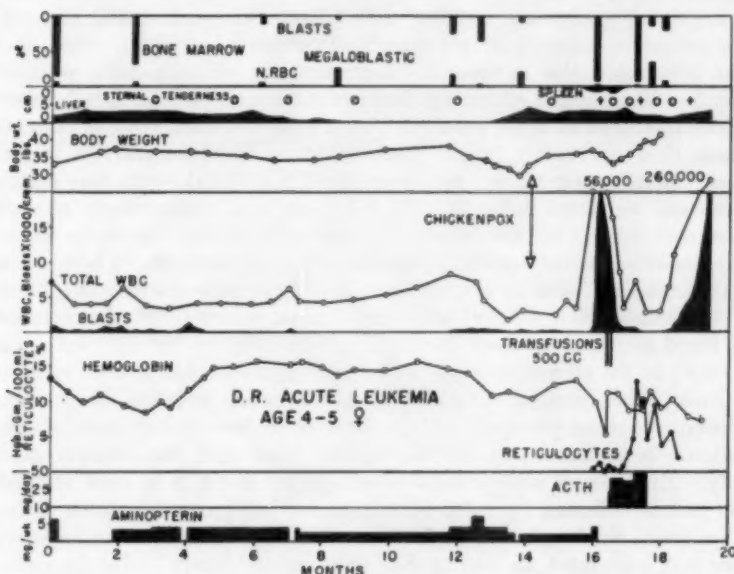


FIG. 10. Course of a patient (D. R.) with acute lymphoblastic leukemia treated successfully with Aminopterin for more than a year. The remission induced with ACTH, after Aminopterin resistance had developed, was very brief.

recently, the folic acid antagonists,⁹ ACTH and cortisone,¹⁰ and a purine antagonist, 6-mercaptopurine.¹¹

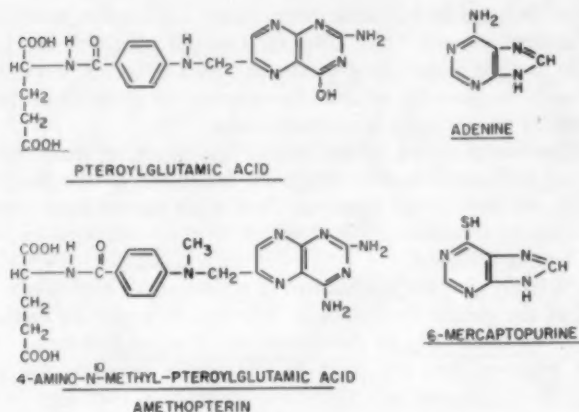
The folic acid antagonists apparently block the conversion of folic acid to folinic acid; Aminopterin and A-methopterin also act as competitive inhibitors of the citrovorum factor. It is very likely that a basic part of the mechanism of action of the anti-folic acid drugs is interference with the synthesis of nucleic acids.

A number of folic acid antagonists have been employed therapeutically, but Aminopterin (4-aminopteroyl glutamic acid) and A-methopterin (4-amino, N¹⁰-methylpteroylglutamic acid) have gained the widest trial. It has been demonstrated clearly that the use of these agents may be associated

with a dramatic remission even in a moribund child. The blood picture returns toward normal and may become entirely normal. With this the bone marrow picture may approach or attain a normal pattern (figure 10). The associated clinical improvement is striking: fever and hemorrhagic manifestations disappear, as do the visceral enlargement and lymphadenopathy, and the patient may seem to be entirely well. Unfortunately, this excellent effect is only temporary and does not occur at all in some cases. Furthermore, it is unusual in adults. A complete clinical and hematologic remission has been observed in about one third of affected children. Partial hematologic response together with substantial symptomatic improvement occurs in another 20 per cent.²³ However, remissions, when they occur, are measurable in months. Unfortunately, retreatment is progressively less effective and ultimately the patient becomes completely refractory.

The treatment of acute leukemia with a folic acid antagonist is not easy because these agents are toxic. Their effect on the bone marrow is profound. Severe pancytopenia can be produced and megaloblasts may replace the normal nucleated red cells. At the same time hemorrhagic necrosis of the epithelium of the alimentary tract may occur, as manifested by ulcerative stomatitis, gastrointestinal symptoms or bloody diarrhea. These agents are particularly difficult to employ in the acutely ill patient with much bleeding and leukopenia. Several weeks may ensue before benefit is observed, and blood transfusions must be the chief mainstay in the interval. The discovery of the effectiveness of ACTH and cortisone has proved to be of particular value, therefore, since these agents, when effective, bring about improvement more promptly and at the risk of less serious toxic efforts. Cortisone is preferable, of the two agents, since it is conveniently taken orally. Evidence of improvement often appears in the first week of treatment and is indicated by a decrease of hemorrhagic manifestations, reduction of fever, development of a sense of well being and a fall in the leukocyte count if it is elevated, as well as disappearance of "blasts." By the end of the second week the platelets begin to increase, as does the hemoglobin.

It is generally stated that clinical improvement is demonstrable in about 70 per cent of previously untreated cases of acute leukemia, with complete hematologic remissions and clinical remissions occurring in half this number. We have been impressed with the strikingly uniform beneficial effects of hormone therapy in cases of acute lymphoblastic leukemia and its failure in the other forms.²⁴ While mention of this difference in effect can be found in publications by various investigators,²⁵ the observation has not been stressed and little attention has been given to the selection of cases for hormone therapy. We have been so impressed with the failure of hormone therapy in myeloblastic and in monoblastic leukemia, as well as with the fact that in some cases the condition of the patient has become worse in the course of such treatment (figure 12), that we regard its use as contra-indicated in these types of acute leukemia.



FOLIC ACID AND PURINE ANTAGONISTS

FIG. 11. Chemical structures of A-methopterin and 6-mercaptopurine.

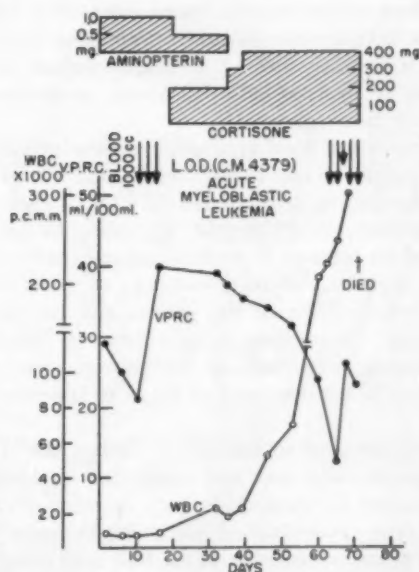


FIG. 12. Course of a patient (L. O. D.), 29 years of age, with acute myeloblastic leukemia who clearly improved on Aminopterin therapy. Treatment with cortisone was instituted in the hope that a prolonged remission might be produced; instead, rapid deterioration took place.

Remissions induced by hormone therapy may last but two to three weeks, or as long as nine months. Second remissions, if obtained, are less complete than the first; in these cases hydrocortisone has been of no more value than cortisone. In general, refractoriness seems to occur more readily to cortisone than to the anti-folic acid compounds.

The mechanism of action of the steroid hormones in acute leukemia is obscure. The difference in the results of treatment in the several types of leukemia is not surprising, however, since these agents have been shown to be myelopoietic stimulants,²⁶ in contrast to their effect in causing dissolution of lymphoid tissue.

Since it is likely that the mechanism of action of the anti-folic acid compounds and of the steroid hormones is different, it would be logical to use these agents simultaneously in the treatment of acute leukemia. In practice, such a regimen does not seem to offer more than the use of either drug alone. It is our custom, therefore, to employ cortisone initially in the treatment of acute lymphoblastic leukemia, since its action is quicker than that of the folic acid antagonists, subsequently replacing the cortisone with A-methopterin after a complete remission has been obtained. The dose of cortisone is that amount necessary to produce a remission, often 150 mg. per day but even as much as 300 mg., even in children. The daily dose is given at three or four evenly spaced intervals. Potassium chloride, in tablets of 0.3 or 1.0 gm. size, should be taken also, in doses of 3 to 6 gm. daily, as well as a low salt diet (1 to 2 gm. sodium chloride per day). Although evidence of hypercorticism develops, no serious ill effects have been encountered on this regimen.

When a remission has been attained, the dose of cortisone is reduced gradually in the course of one to two weeks and A-methopterin is given instead, in amounts ranging usually from 1.25 to 5.0 mg. per day by mouth. The dose of A-methopterin is "titrated" according to the clinical condition of the patient, and an attempt is made to steer between the production of toxicity and the maintenance of normality, an objective which can be attained only by examination of the patient and his blood at weekly or fortnightly intervals. In addition to the number of "blasts" and the leukocyte count, the hemoglobin level and the platelet count are important as guides. We do not find it necessary to resort to bone marrow examination very often.

In acute myeloblastic or monoblastic leukemia the choice lies between a folic acid antagonist and a new anti-metabolite, 6-mercaptopurine (figure 11). With any agent the outlook is poor in monocytic leukemia, but in the myeloblastic type remissions of some degree have been observed in about 25 per cent of cases treated with the folic acid antagonists.²⁷

Good clinical and hematologic remissions were observed by Burchenal et al.²¹ in 15 out of 45 children with acute leukemia treated with 6-mercaptopurine, in an occasional adult and, what is more significant, in 20 to 45

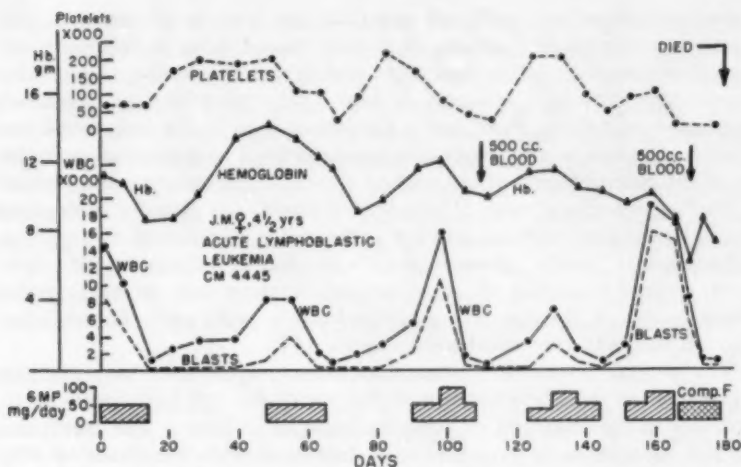


FIG. 13. Effect of 6-mercaptopurine in a child (J. M.) with acute lymphoblastic leukemia who failed to respond to cortisone and A-methopterin therapy after a year of successful management.

per cent of patients who had become resistant to the anti-folic acid agents or to cortisone. The drug has also been observed to produce a temporary remission in both the early and the late stages of chronic myelocytic leukemia.

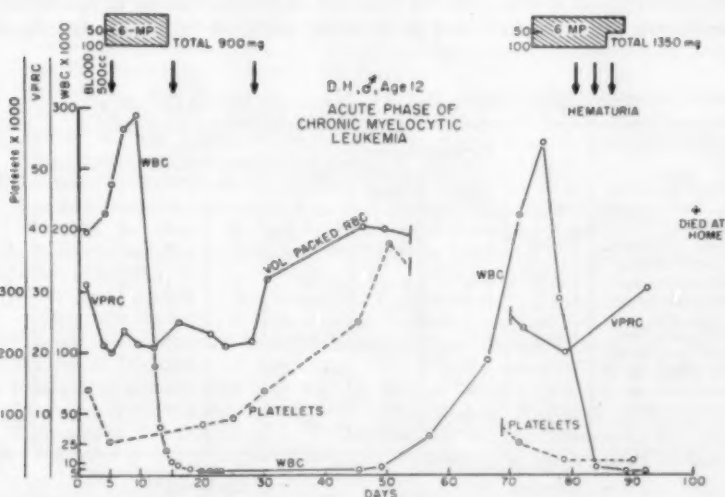


FIG. 14. Effect of 6-mercaptopurine in a boy with chronic myelocytic leukemia of 20 months' duration in the final "myeloblastic" phase.

Our own experience with this agent has not been as successful as this. In only two out of 10 children, previously treated with other agents, did a complete remission follow treatment with 6-mercaptopurine (figure 13). Partial remissions were observed in four. Of nine adults, all previously untreated except three, there was a significant drop in the leukocyte count in seven. In two of these cases this was associated with a reduction in the size of the enlarged organs and general clinical improvement with decrease in bleeding manifestations. These partial remissions lasted a very short time in one patient and two months in the other. In one of two patients in the terminal "blastic" phase of chronic myelocyte leukemia, a very satisfactory partial remission of seven weeks' duration was achieved, and a second course of therapy was associated again with some improvement, although this was very short-lived (figure 14).

The over-all results of treatment with 6-mercaptopurine have not been as favorable as those associated with the use of the anti-folic agents or the hormones in the treatment of acute leukemia in children. The compound, however, does seem to have a place in treatment when resistance to other agents has developed in children. It also deserves a thorough trial in the treatment of affected adults and in patients of all ages who have myeloblastic leukemia, even possibly as the agent of choice.

CONCLUSIONS

Table 1 summarizes the experience and recommendations which have been discussed above. The discussion has been concerned chiefly with chemotherapy. It is not intended to imply, however, that radiation therapy is now outmoded. As indicated in the table, radiation therapy is as valuable

TABLE I
Summary of Chemotherapy of Leukemia and Related Disorders

Disease	X-ray pa	Mustard Congeners		Myleran	Urethane	Folic Acid Antagonists	Cortisone ACTH	6MP
		HN ₂	TEM					
Hodgkin's	++++	++++	++++	0	0	C	±	C
Chronic lymphocytic leukemia	+++	++	+++	0	0	C	±	C
Lymphosarcoma	+++	++	++	0	0	C	±	C
Reticulum cell sarcoma	++	++	+	0	0	C	0	C
Chronic myelocytic leukemia	+++	+	+	++++	++	C	C	+
Acute leukemia—								
lymphoblastic	C	C	C	0	0	++++	++++	++
myeloblastic	C	C	C	0	0	+++	C	++
monocytic	C	C	C	0	0	+	C	+

++++ Effective and preferable
 +++ Effective
 ++ Moderately effective
 + Slightly effective

± Sometimes effective
 0 Ineffective
 C Contraindicated

as any of the chemotherapeutic agents in the treatment of all the conditions listed except acute leukemia. In some conditions radiation therapy may be more effective than any of the chemical compounds which have been discovered so far. Thus, it has yet to be shown that the remissions induced by Myleran are comparable in duration to those which follow skillful radiation therapy. Again, radiation locally applied when no systemic therapy seems to be required has no counterpart in chemotherapy. Against these advantages must be weighed the convenience and smaller cost of chemotherapy and the discomforts of radiation sickness as compared with those of the drugs which may be used. In the last analysis, the most effective management of the disorders under consideration is to be found in the judicious use of the whole therapeutic armamentarium that is available.

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THE RIDDLE OF SARCOIDOSIS (HUTCHINSON-BOECK GRANULOMATOSIS) *

By WILLIAM S. MIDDLETON, M.D., M.A.C.P., *Madison, Wisconsin*

TRADITIONALLY, the medical literature has been embellished by the liberal utilization of eponyms. The names of the inventors of instruments cling tenaciously to their brain children for generations. Symptoms, signs and diseases bear their discoverers' names to posterity. On occasions this time-honored formula may misdirect the credit for priority, but in this materialistic period of medicine it at least lends a human touch that is sorely needed. Furthermore, the curious minded may be stimulated by this circumstance to explore the sources of such eponyms. Indeed, they may afford invaluable building stones in the reconstruction of the historical evolution of the knowledge of the given medical subject.

In no disease will this pursuit prove more rewarding than in sarcoidosis. In all, some 20 different designations have been given to this disorder. With nationalistic fervor, a number of these terms are eponyms designed to accord the distinction of priority, viz., Boeck's, Besnier's, Tenneson's and Schaumann's disease. Though each of these clinicians made his contribution to the sum of the knowledge of this disease, Hutchinson¹ first described and depicted its cutaneous manifestations in 1875. Twenty-three years later Hutchinson² reported further instances of the disorder under the term "Mortimer's malady," in recognition of a patient so affected. Boeck (1899)³ was the first to designate the disease of the skin and mucous membranes as "sarcoid." His choice of this word was purely descriptive. In 1889 Bésnier⁴ had delineated lupus pernio, and in 1919 Jüngling⁵ described certain osseous lesions under the impressive term of "Ostitis tuberculosa multiplex cystica." Heerfordt (1909)⁶ afforded a classic description of a syndrome with involvement of the salivary glands and the uveal tract under the designation of "Febris uveo-parotidea subchronica." Schaumann (1914)⁷ first appreciated the histologic unity of lupus pernio and sarcoid. Furthermore, he extended the range of the observations of this lesion from the skin, mucous membranes, bones and lymph nodes to widespread visceral encroachment by the same process. To differentiate this condition from Hodgkin's disease, he suggested the term "benign lymphogranuloma."⁸ Bruins Slot (1936)⁹ first identified uveoparotid fever as a manifestation of this disease. In 1936 Hunter¹⁰ gave the designation "generalized 'sarcoidosis'" to this disorder. The trend of recent years has been toward a broadening of the diagnostic base.

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In attempting to resolve the confusion of nomenclature, the Conference on Sarcoidosis convened by the National Research Council, February 11, 1948, in Washington, D. C., offered the following definition: "Sarcoidosis is a disease of unknown etiology. Pathologically, it is characterized by the presence in any organ or tissue of epithelioid-cell tubercles with inconspicuous or absent necrosis, and by the frequent presence of refractile or apparently-calcified bodies in the giant cells of the tubercles. The characteristic lesion may be replaced by fibrosis, hyalinization, or both."

This characterization affords a logical approach to the more detailed consideration of the pathology of sarcoidosis. The pathologic unit of this singular disease is the so-called firm or hard epithelioid-cell tubercle, in which small areas of necrosis with giant cells may appear. True caseation does not occur. Inclusion bodies are noted in the protoplasm of the giant cells. These may consist of irregular basophilic staining material in concentric rings, clearly staining flat plates and asteroid bodies, lying in a vacuole within the protoplasm of the giant cell (Schaumann).¹¹ Chronologically, a conspicuous feature of sarcoidosis is its sluggish course. Progress studies may show little change over months or years. Apparently normal lymph nodes may contain the classic epithelioid reactions of sarcoidosis. With the advancing knowledge of this subject, practically no tissue of the body has escaped involvement. The classic lesions may be microscopic in size or may develop into massive granulomatous conglomerations. In the process of resolution, thickening of the reticular network with advancing fibrosis to hyalinization is the rule. In the occasionally fatal subject of this disease, intercurrent infection, tuberculosis or serious involvement of some vital organ or tissue, as the myocardium or the brain, by sarcoidosis itself has proved the determining lethal factor.

Much of the confusion that has attended the study of sarcoidosis has arisen from its designation. Boeck³ was unquestionably prompted to term it "sarcoid" by the superficial similitude of its histologic appearance to sarcoma. Actually, its resemblance to sarcoma stops there, for there is nothing in its pathologic sequence or clinical picture to suggest a relationship. A continuing source of error is the failure to differentiate between a local sarcoid reaction and sarcoidosis. Nichol and Dominguez¹² described a cutaneous granuloma from a contamination with beryllium phosphors. German¹³ encountered a granulomatous lesion of the scalp in a mountain climber who had sustained a lacerated wound from stones in a fall. The presence of silica crystals in the granuloma led to their incrimination in a causal relation. Refvem¹⁴ adduced evidence that certain granulomata in the intestinal tract arose from foreign bodies. Among these granulomata in the anorectal region, talcum was an important constituent. In the present relation, his observation of crystalline material in the nodules of four patients with a histologic picture of sarcoidosis deserves especial attention. In two instances of the pulmonary form of the disease, the inhalation of chalk dust was held responsible. Furthermore, from other reports

the granulomata of brucellosis, tuberculosis, leprosy, leishmaniasis and fungus infections may be indistinguishable from the epithelioid-cell tubercle of sarcoidosis. The counterfeiting may add inclusion bodies. Engle¹⁵ carefully characterized the histologic pictures of "sarcoid and sarcoid-like" granulomata. Pinner¹⁶ trenchantly expressed his reservations: "One or two single but diagnostically unquestionable foci certainly do not justify the diagnosis of sarcoidosis. The pathologist who is confronted with a biopsy specimen containing a few characteristic sarcoid tubercles should probably report no more than 'sarcoid tubercles'; he can not know whether the patient has sarcoidosis." As a consultant, the pathologist should have the advantage of the complete clinical and laboratory findings to insure, if possible, the distinction between a local sarcoid reaction and widely dispersed sarcoidosis.

The specific etiology of sarcoidosis has not been fixed. Certain predisposing factors are generally accepted. Although the North Temperate Zone has been the area of its greatest reported incidence, sarcoidosis has been encountered over the entire civilized world. Studies in the United States Army indicated an incidence of sarcoidosis 17 times as common in the Negro as in the white race. In an epidemiologic study Michael, Cole, Beeson and Olson¹⁷ quoted Ransmeier's evidence for a high incidence of this disease in natives of the southeastern portion of the United States. This circumstance applied to the white as well as to the Negro race. The rate for all white inductees was 0.88 per 100,000, as compared with 17.81 for all Negroes. Among those of Southern origin the rate was 2.24 per 100,000 for the white race and 24.63 for the Negro. The incidence was definitely higher among those of rural origin. Although the disease has been encountered in siblings (Robinson and Hahn),¹⁸ there is no convincing evidence of its communicability. In general, the sex distribution may be said to be equal.

The possible relationship of sarcoidosis to tuberculosis is an unsettled issue which has received critical attention from Pinner,¹⁹ Rostenberg,²⁰ Longcope and Freiman,²¹ and others. Perhaps one of the most interesting commentaries in this direction has been the appreciable decrease in the diagnosis of hyperplastic tuberculosis with the increased recognition of sarcoidosis. In general, efforts to culture the *Mycobacterium tuberculosis* from the lesions of sarcoidosis have been futile. The occasional demonstration of a nonviable acid-fast bacillus in the lesions has been unconvincing. Animal inoculations of macerated sarcoid tissue have failed to fulfill Koch's postulates. The oft quoted experience of Kyrle²² has not been duplicated. Indeed, Pautrier²³ disqualified the evidence on material grounds. The *Mycobacterium tuberculosis* was isolated by Kyrle from the cutaneous lesion on the tenth day. These organisms had disappeared from the lesion on the thirty-sixth day and the infiltration had undergone involution by the ninety-fourth day. Finally, one of two guinea pigs inoculated with the blood of the patient died of tuberculosis. Certainly these circumstances

support the diagnosis of tuberculosis in a stage of bacillema rather than sarcoidosis. To this date, neither human, bovine nor avian forms of the *Mycobacterium tuberculosis* have been established as the specific etiologic agent in sarcoidosis. Nor, for that matter, have we sustained evidence that the product of any of these organisms is responsible for this disease.

The low incidence of positive tuberculin reactions among patients with sarcoidosis has led to much study and discussion. The Jadassohns' ^{24, 25} explanation of a positive anergy won much support; but subsequent work has, in the main, refuted this theory, which held that the rapid destruction of tuberculin gave no opportunity for the cells of the host to react. In a series of 20 patients with sarcoidosis, Israel, Sones, Stein and Aronson ²⁶ encountered an inability to develop and to maintain a skin sensitivity to BCG vaccine. In their judgment, this circumstance represents a nonspecific tuberculin anergy from an interference with the general immunologic mechanism. Recent observations (Urbach, Sones and Israel) ²⁷ have demonstrated the ability to transfer tuberculin sensitivity passively by living white blood cells to tuberculin-negative controls. These results were duplicated in six tuberculin-negative patients with sarcoidosis. White blood cells from patients with sarcoidosis did not inhibit the tuberculin reaction in known reactors. While the absence of anticutins or other inhibiting factors to the tuberculin reaction does not rule out tuberculosis as a cause of sarcoidosis, it minimizes the theory of unusual antibodies in such subjects. Friou ²⁸ directed attention to the singular lack of cutaneous reactions to Oidiomycin, trichophytin and mumps virus antigen in patients with sarcoidosis. This circumstance was more conspicuous in tuberculin-negative patients. Sones and Israel ²⁷ extended these observations to include pertussis agglutinin. The normal responses of their subjects in circulating antibodies to pertussis agglutinin and typhoid vaccine and to the passive transfer of ragweed sensitivity favored the explanation of a local immunologic defect in this disease. Nor is this situation peculiar to sarcoidosis. Notably Schier ²⁹ has reviewed the literature and has established a striking anergy to the antigens of mumps virus, *Candida albicans* and *Trichophyton gypseum*, and to purified protein derivative of tuberculin in patients with Hodgkin's disease. The tuberculin anergy in sarcoidosis appears to be nonspecific and, in a measure, dependent upon the reticuloendothelial involvement in this disease. The suggestion of a "terrain sarcoidique," while inviting, has only theoretic details in its favor.

The moot question of the etiology of sarcoidosis has been subjected to serious review and study. ^{16, 19, 20, 21, 31} Among other provocative experiences Jaques ³⁴ encountered generalized sarcoidosis in an adolescent girl in whom the reaction to nematode larvae was established as the etiologic background. The histologic picture included Schaumann bodies. Obviously, only the nematodes with a systemic phase in their life cycle, i.e., *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Necator americanus* (or *Ancylostoma duodenale*), could offer such a dissemination with pulmonary

involvement. Jaques⁸⁷ adduced further supportive evidence of a nematode responsibility in isolated instances of the disorder. He concluded "that sarcoidosis results from an altered capacity of the host to react to various as yet unidentified antigenic substances, one of which may result from nematode infestation." Reimann and Price⁸⁸ reported the confusion of the histology of histoplasmosis with sarcoidosis. So the incriminated agents might be multiplied. Rostenberg²⁰ has afforded a constructive critique of this aspect of the subject. After weighing the available evidence from every conceivable angle, he decided "that the most likely cause is a new infectious agent."

In a thoughtful survey of the hepatic involvement in sarcoidosis, Branson and Park²⁸ summarized the situation as follows: "The key to the riddle of etiology, the answers to the questions concerning the mechanism of the formation of the tubercles and tissue specificity and selectivity whereby tubercle growth is accepted or rejected, and the solution to the problems of specific treatment and prevention, all lie in the future." In essence, the evidence for the tuberculous etiology of sarcoidosis is deficient in certain essential details. Whatever may be the etiologic agent, the anergy to tuberculin appears to be nonspecific. After due deliberation, Longcope and Freiman²¹ wrote: "It seems probable, however, that an open mind and new methods of approach such as are suggested by the Kveim reaction, for example, may eventually prove more profitable than endless wrangling over the role of the tubercle bacillus in the etiology of sarcoidosis."

In 1935 Williams and Nickerson²⁹ proposed a cutaneous test for sarcoidosis after the manner of the Frei reaction. The antigen was prepared by macerating an excised cutaneous lesion in sterile sand and normal saline solution. After sterilization, intracutaneous injections were made in four patients with recognized sarcoidosis. All responded by the development of a red papule and a zone of erythema at the site of the injection. Four control subjects without sarcoidosis showed no response. Unfortunately, all of the reactions occurred within 24 to 36 hours, a circumstance that seriously detracts from their significance. Kveim³⁰ prepared similar antigens from the lymph nodes of patients with sarcoidosis. The histologic picture of sarcoidosis was reproduced in certain of the local reactions in weeks to six months after the injections. In general, the correlation of positive reactions with the clinical and pathologic diagnosis is very high. Nitter³¹ recently reported 77 per cent positive reactions among 79 patients with proved sarcoidosis. These results confirm the earlier reports of Putkonen³² and Danbolt and Nilssen³³; but the difficulties attendant upon the preparation of the antigen, its variability dependent upon the source, and the long period of incubation have limited its application in this country. Furthermore, Nelson³⁴ has disclosed the disquieting factor of an occasional similar reaction to antigens produced by the extraction of the normal spleen. The Kveim reaction has not solved the enigma of the etiology of sarcoidosis.

Few diseases have as protean clinical expressions as sarcoidosis; yet,

one of the most singular details within its manifestations paradoxically is the frequency of its clinical silence. Perhaps this circumstance might be anticipated from the indolence of the histologic unit. Even to the diagnostically conscious clinician, the extent of pulmonary or other visceral involvement without constitutional reaction and symptomatology comes as a sharp surprise. The comprehensive articles by Pinner,¹⁹ Longcope,²⁰ Freiman²⁶ and Jaques²⁷ have adequately reviewed the literature of sarcoidosis. Its monographic consideration by Longcope and Freiman²¹ admirably consolidated the information on the clinical aspects of the disease, so that it is beyond the purview of the present consideration to exhaust the several organic and systemic manifestations of the disease. Rather, certain isolated expressions will be considered to disclose its singular nature.

The cutaneous manifestations of sarcoidosis were the first to attract clinical attention. Boeck² gave the classic description of the small and large nodules in the butterfly area of the face, on the arms and back, and the diffuse infiltrative lesions of the nose, face and ears. The skin over the affected area may appear tense and bluish to purplish, with tiny, yellow granules at the margin. Atrophic scars may mark the scene of earlier lesions. Recent attention has been paid to the occurrence of erythema nodosum in patients with sarcoidosis. Löfgren²⁸ analyzed a total of 178 patients with erythema nodosum, among whom six (3.4 per cent) suffered from sarcoidosis. As a rule, these patients have marked lymphadenopathy of the tracheobronchial nodes. Indeed, pressure from this source may induce an irritative harassing cough or serious dyspnea. Yet fever and other constitutional symptoms are minimal. The absence or the mildness of attendant symptoms and the indolence of the accompanying lymphadenitis should be guides to the consideration of this etiology.

Uveoparotid fever (Heerfordt, 1909), which constitutes one of the most unusual manifestations of sarcoidosis, may be defined as an inflammatory and granulomatous involvement of the uveal tract, and the parotid and other salivary glands, complicated by involvement of the facial nerve and, less commonly, other cranial nerves. A disease of adolescents and young adults, it is usually initiated by fever, lassitude and drowsiness. Gastrointestinal symptoms, anorexia, nausea, vomiting and diarrhea may supervene. Fever, night sweats, arthralgia and paresthesia are not infrequent. Puffiness of the eyes occasionally occurs. As a rule, enlargement of the parotid glands, simultaneous or unilateral, precedes involvement of the uveal tract. The parotid gland is firm, nodular and painless in this involvement, but there may be some tenderness. Mastication is rarely impaired. The other salivary glands may occasionally be involved. When invasion of the lacrimal glands occurs simultaneously, the picture of Mikulicz's syndrome is reproduced. The salivary glandular involvement may persist for from a few weeks to upward of two years. With its subsidence, a permanent induration may remain. Soreness of the eye should lead to a suspicion of uveal tract involvement, since conjunctivitis commonly precedes the

latter. As a rule, the eventual iridocyclitis is bilateral, although one side may anticipate the other. Posterior synechiae of the iris may develop. Vitreous opacities occur in about one-half of the patients, and permanent impairment of the visual acuity is not infrequent. Total blindness may be occasioned by such complications as corneal opacities, vitreous hemorrhage, optic neuritis, neuroretinitis, chorioretinitis, glaucoma, aqueous turbidity and cataracts. Seventh nerve paralysis, unilateral or bilateral, may appear suddenly a few days to a few months after the onset of the parotitis. The lower facial distribution is more seriously affected than the upper, and in the convalescence this will be the last to improve. An occasional paralysis of the soft palate with dysphagia, intercostal neuralgia, paralysis of the vocal cords, deafness, ptosis of the eyelid, wasting of the muscles of the hand, loss of vibratory perception in the legs and polyneuritis may be clues to widespread but spotty neural involvement.

Increasing attention has been paid to the pulmonary involvement of sarcoidosis in recent years. The widespread utilization of roentgenography in the screening of inductees in the Armed Services in World War II and the extension of this program to civilian life in a number of relations have undoubtedly afforded one of the greatest boons to the study of pulmonary sarcoidosis. The asymptomatic order of a majority of the subjects of this disorder, in spite of relatively extensive or actually massive involvement, has been most revealing. A minority of these patients, particularly those with progressive pulmonary lesions, will experience fever, night sweats, weight loss and easy fatigability. Upon more careful questioning, dyspnea of advancing degree may be elicited. Cough eventually becomes a presenting symptom if the process be progressive. Occasionally hemoptysis may appear. Pleuritic pain is uncommon.

The roentgenologic evidences of pulmonary involvement may afford the first and the most impressive signs of sarcoidosis. In an exhaustive study of 90 patients with pulmonary sarcoidosis, Nitter³¹ divided the classic roentgenologic findings into five stages:

"Stage I: Bilateral hilar lymphadenopathy alone, or with associated paratracheal lymphadenopathy, without parenchymal involvement (adenopathy of same appearance as that of Stage II).

"Stage II: Bilateral lymphadenopathy, with accentuation of perihilar markings, with or without associated paratracheal adenopathy.

"Stage III: Diffuse pulmonary nodulation, i.e., parenchymal densities varying from 3 to 5 mm. in diameter, or more.

"Stage IV: Disseminated miliary lesions, i.e., parenchymal densities of about 1 mm. in diameter, simulating those of a miliary tuberculosis.

"Although persistence of hilar and paratracheal lymphadenopathy may be observed in some instances, these changes will usually be gone or

showing marked regression by the time of Stage III or Stage IV involvement.

"Stage V: The stage of fibrosis, with fibrotic changes involving the living parenchyma."

In all pulmonary sarcoidosis the more or less massive and symmetrical enlargement of the lymph nodes of the hila and bilaterality of the pulmonary involvement may be anticipated. Nitter³¹ differed with most students of this area in considering the various appearances merely stages of a single basic process. Its indolence and slow metamorphosis over months or years may afford added clues to the diagnosis. Emphysema and advancing fibrosis may lead to distortion and displacement of the trachea and mediastinal structures. As a direct reflection of the increased intrapulmonic circulatory load, chronic cor pulmonale may supervene. Bronchiectasis and superimposed infection are not infrequent. A rapid termination may result from pulmonary tuberculosis in such patients.

Perhaps the area of greatest interest in the evolution of the knowledge of sarcoidosis has been the growth in the appreciation of the cardiac involvement. The impact of pulmonary fibrosis upon the heart, with the resultant chronic cor pulmonale, has long been appreciated. However, Salvesen's observation of an independent myocardial involvement³⁹ with bundle branch block attracted little clinical attention for some years. Longcope and Fisher⁴⁰ found six instances of myocardial or pericardial involvement among 31 patients with sarcoidosis. The clinical evidences of cardiac involvement ranged from minor changes to serious handicaps in enlargement of the heart and arrhythmia, with electrocardiographic corroboration. Of these six patients, at necropsy three disclosed serious invasions of the myocardium and pericardium by sarcoidosis. Accumulating evidence would indicate that, while not a frequent complication or determining factor in disability in sarcoidosis, myocardial invasion is nonetheless a very serious site of predilection for this lesion. Scattered epithelioid bodies may lead to minor conduction faults or tachycardia. Paroxysmal tachycardia, ectopic beats, bundle branch block, and varying degrees of auriculoventricular dissociation to complete heart block have been recorded. Massive infiltration of the myocardium by such granulomatous lesions may result in progressive cardiac failure or sudden death.⁴¹ Indeed, so important is this aspect of the total picture as to require electrocardiographic study in any patient with sarcoidosis who manifests persistent tachycardia or arrhythmia.⁴²

The hematopoietic impact of sarcoidosis has received scattered attention over the years. Doan and Wright⁴³ indicated that sarcoidosis was an occasional cause of hypersplenism. Bruschi and Howe⁴⁴ reported an instance of thrombocytopenic purpura in a patient with sarcoidosis whose condition was completely relieved by splenectomy. Dameshek and Estren⁴⁵ reported an instance of splenic pancytopenia with nonhemolytic anemia secondary to splenic involvement in sarcoidosis. This patient experienced an

improvement in the entire blood picture upon splenectomy. Partenheimer and Meredith⁴⁶ added a further instance of hypersplenism due to sarcoidosis, with correction of the leukopenia and anemia after splenectomy. Edwards, Wagner and Krause⁴⁷ recorded a fatal instance of thrombocytopenia in a patient with sarcoidosis of the spleen. These reports do not exhaust the literature, which is still rather desultory on this aspect of sarcoidosis. At the same time, it is appreciated that gross splenomegaly may occur without hematopoietic disorder.

The diagnosis of sarcoidosis presents few difficulties to the diagnostically aware clinician. The racial distribution, age incidence, widespread and diversified manifestations, clinical silence, or paucity of symptoms and signs, negative Mantoux reaction and the indolent course lead naturally to the essential laboratory supportive studies. Weeden and Beckh,⁴⁸ in an analysis of the San Francisco experience, state that the correct diagnosis was first made by the clinician in 48 per cent, the roentgenologist in 10 per cent, and the pathologist in 42 per cent of their patients.

As a rule, the hemogram of the patient with sarcoidosis is not diagnostic. Infrequent instances of hemolytic anemia are encountered. These are currently interpreted as expressions of hypersplenism. The leukocytes are usually within normal range. Occasionally, a slight leukocytosis is recorded. If there be leukopenia, the monocytes may be relatively increased. Eosinophilia of 10 to 16 per cent has been reported. The erythrocyte sedimentation rate is usually increased. The total serum proteins are increased in the majority of instances. In practically all subjects with activity of the underlying condition, the albumin-globulin ratio is inverted through an actual increase in the globulin.⁴⁹ The blood calcium and phosphatase are commonly increased.⁵⁰ The blood serologic test for syphilis is negative. Blood cultures remain negative in the absence of intercurrent bacteremia. Sputum cultures and gastric washings are unsupportive. As indicated, the roentgenogram of the thorax may be startling in its revelation of unsuspected pulmonary and mediastinal involvement. Roentgenograms of the hands and feet should be taken in all suspected subjects, since punched-out areas in the medullary portion of the phalanges, metacarpal or metatarsal bones may afford an early clue to the diagnosis. An escape of the periosteum from this invasion is conspicuous in such sites. The Kveim reaction must be held sub judice. The biopsy affords the clinching diagnostic nail. Obviously, the skin and lymph nodes offer the first approach. The scalene node has been suggested as a useful and relatively accessible source of biopsy material.⁵¹ No longer is the tonsil preferred as a site of histologic study. The bone marrow affords an accessible tissue for appropriate attack.⁵² The spleen is involved in 68 per cent of patients with sarcoidosis, and the liver in 66 per cent.⁵³ By reason of greater accessibility and relative freedom from complications, biopsy of the liver has come to be preferred.

The clinical course of sarcoidosis is quite unpredictable. Apparently mild and innocuous involvement may progress very rapidly to disabling pro-

portions. Conversely, the extensive and massive lesions of this disease may rapidly subside or remain stable for years. Remissions with relapses are not uncommon; but by and large, the indolence of this process usually moves toward a prognosis of healing. A mortality of 5 per cent has been ascribed to this disease. Cowdell⁵⁴ studied the course of 90 patients with sarcoidosis over a period of years. Of this group, 17 died at intervals of up to eight years after the diagnosis had been established. In eight of the patients who died, sarcoidosis was deemed directly or indirectly responsible. Cardiac failure accounted for the fatal outcome in five of these subjects, and the failure was right-sided in four. Leitner⁵⁵ collected 72 fatalities from sarcoidosis in the literature. Cardiac failure led the list, with 26 deaths. Tuberculosis was second, with 12, while sarcoidosis of the nervous system and miscellaneous secondary infections each accounted for nine.

The treatment of sarcoidosis is definitely restricted by reason of the limited knowledge of its true etiology. Many of the measures that have had temporary favor in its management have been discarded. Among these may be listed tuberculin, arsenic, gold, antileprol and ultraviolet rays. In recent years, calciferol and nitrogen mustard have been studied exhaustively. The Army experience would reject nitrogen mustard. Calciferol still has some ardent proponents. The recommended doses—calciferol, 150,000 to 900,000 units, or dihydrotachysterol, 3.75 mg. (reduced to 1.2 mg.) daily by mouth—approach the toxic levels and their effects must be observed carefully to avoid hypercalcemia.⁵⁶ Isoniazid is ineffective in cutaneous sarcoidosis.⁵⁷ Roentgen therapy has been recommended for sarcoidosis,⁵⁸ but recent^{21, 31} reports have not supported its use. Indeed, the pendulum is swinging against deep roentgen therapy in this condition. Sarcoidosis is a benign, self-limited disease in a great majority of instances, and drastic therapeutic measures should be avoided.

The growing literature now weighs the availability of adrenocorticotropin and cortisone. Unfortunately, the experience with these potent agents has not been consolidated. McClement, Renzetti, Himmelstein and Courmand⁵⁹ made some interesting studies of the effect of cortisone upon the cardiopulmonary function of patients with pulmonary sarcoidosis. Physiologic improvement occurred in two of these subjects with alveolar-capillary oxygen diffusion impairment, and in one with an emphysema-like pattern. In general, the experience has indicated early improvement under cortisone therapy if initiated in the proliferative or active stage of the disease in any tissue or organ. This advantage is not ordinarily maintained upon withdrawal of the support, and relapses are the rule. In the manifest involvement of the skin and accessible lymph nodes, such results may be clearly evaluated by observation and biopsy. Inaccessible lesions are less readily evaluated; but there has been accumulating evidence that the more progressive pulmonary infiltrates may undergo resolution under cortisone therapy. Relapses even in such processes usually occur upon withdrawal of the steroid. It is possible that a readjustment of dosage and longer

continued and smaller amounts of cortisone may be a partial answer to this disquieting experience. The topical application of cortisone may be useful in the treatment of cutaneous sarcoidosis.⁶⁰ Certainly, the status of cortisone therapy is still unsettled insofar as the cutaneous, lymphatic, osseous and visceral forms of the disease are concerned. The situation relative to the place of cortisone therapy in uveoparotid fever is entirely different. While the neural and salivary gland involvement may follow the pattern of responses elsewhere in the body, a dramatic improvement of the uveitis upon the topical application of cortisone has been the rule.⁶² Certain reports give equally good results from the oral use of cortisone in this form of sarcoidosis, but Shulman, Schoenrich and Harvey⁶³ observed these favorable results only in those patients with recent lesions of the uveal tract. None of their patients developed tuberculosis, but this complication must be borne in mind whenever adrenocorticotropin or cortisone is administered. If clinical tuberculosis be recognized or suspected, the protection of streptomycin or isoniazid should be sought in the utilization of cortisone.

In addition to such measures, general hygienic care, including particular attention to nutrition, should be enjoined. The avoidance of exposure to tuberculosis need scarcely be cited, since complicating tuberculosis may assume a fulminant and devastating form. Under no circumstances, therefore, should the patients with sarcoidosis be committed to a tuberculosis sanatorium.

In summary, the riddle of sarcoidosis begins with its designation. Neither its etymologic origin nor its derived connotation is clarifying. Until a better term is fixed by a clear definition of its order, the eponym Hutchinson-Boeck granulomatosis would have the advantages of historical accuracy and sharper delimitation. This designation affords a closer link with the conventional terms than Leitner's suggestion of epithelioid-celled reticuloendotheliosis or granulomatosis.⁵⁵ At the same time it avoids a purely pathologic terminology for a clinical entity. In spite of extended studies, the etiology of Hutchinson-Boeck granulomatosis remains an enigma. Although its cause has escaped detection, the evidence of its independent order is growing. In spite of indubitable histologic parallelisms, the responsibility of known bacterial infections, as tuberculosis, leprosy and brucellosis, fungus invasions, as histoplasmosis and toxoplasmosis, infestations, as leishmaniasis and helminthiasis, and particulate matter, as talc, silica dioxide and beryllium phosphors, for this widespread reaction has largely been dispelled. The protean clinical manifestations of this condition may be predicted from its extended involvement of virtually every tissue in the body and its indolent histologic progress. Its benignity has undoubtedly greatly reduced the reported incidence; but diagnostic awareness and the increased utilization of laboratory supports, especially roentgenograms of the thorax, will markedly increase its recognition in the future. Especially stressed are the involvement of the uveal tract and salivary glands, the lungs, hematopoietic system and the heart, since the common-

place cutaneous lymph node and osseous manifestations may be overemphasized in medical thinking. The therapy of Hutchinson-Boeck granulomatosis is disappointing in many respects. Adrenocorticotropin and cortisone have a definite but limited place in the treatment of its early stages. Especial attention should be directed to the brilliant results in the control of the ocular phase of uveoparotid fever by these drugs. As a tool, these therapeutic agents may eventually afford the decisive key to the etiology and the pathogenesis of Hutchinson-Boeck granulomatosis.

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SIGNIFICANCE OF HEMOPTYSIS IN APPARENTLY INACTIVE PULMONARY TUBERCULOSIS *

By ROBERT CHARR, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

Does hemoptysis in patients with apparently inactive pulmonary tuberculosis mean relapse of tuberculosis? If not, what other pulmonary diseases are the causes? How frequently is the hemoptysis unexplained? What is the usual outcome? With these questions in mind, the present study was carried out.

MATERIAL STUDIED AND FINDINGS

The clinical material studied consisted of 123 patients, 54 men and 69 women. In all of these patients the tuberculosis had been considered inactive for the past five to 20 years. Twenty-one—11 women and 10 men—had hemoptysis. Of the total, in 13 the hemoptysis could not be explained. The roentgenologic examination of the chest, sputum examination for tubercle bacilli, and bronchoscopic as well as bronchographic studies were inconclusive; these patients returned to work within a week or two after the cessation of hemoptysis without subsequent relapse. In only three did the hemoptysis mean relapse of tuberculosis:

CASE REPORTS

Case 1. A 50 year old man had had clinically inactive pulmonary tuberculosis for 10 years. In May, 1953, he suddenly developed profuse hemoptysis, bringing up mouthfuls of blood, over a period of three days. A roentgenogram (figure 1) showed, in addition to apical lesions, a nodule at the left hilum. The impression was that the lesion was either tuberculosis or bronchogenic carcinoma. The sputum examination was negative for tubercle bacilli. The bronchoscopic examination, plus a study of the bronchial secretion, was negative for carcinoma. However, the roentgenologic appearance of the lesion was so suggestive of a new growth that the lung was removed. The lesion was a cavity containing caseous material which showed tubercle bacilli.

The hemoptysis in bronchogenic carcinoma is usually not profuse. In this patient the hemorrhage was massive, lasting for several days. In retrospect, this fact should have been counted against the diagnosis of carcinoma. The patient is well at present.

In five patients, the hemoptysis was due to diseases other than tuberculosis:

Case 2. A 50 year old man developed tuberculosis in 1938. He has been well and working for the past 13 years except for repeated attacks of massive hemoptysis,

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which have occurred every two or three years. Between the attacks the roentgenograms of the chest (figure 2) have shown nothing unusual, other than a well circumscribed lesion in the middle third of the left hemithorax with some fibrosis. The last episode was in September, 1952. At that time a careful bronchoscopic examination revealed nothing other than some reddening of the bronchial mucosa on the left

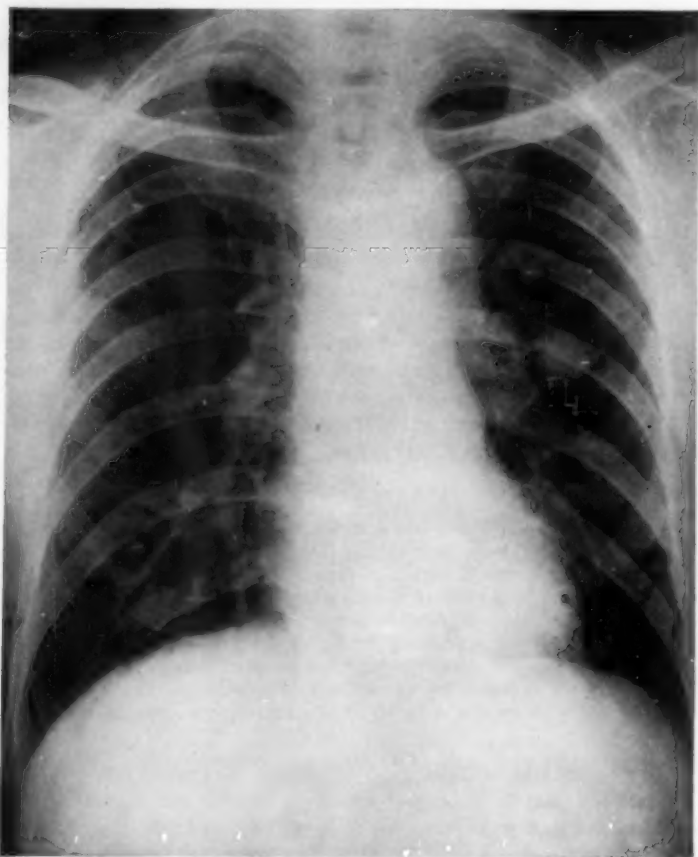


FIG. 1. There is minimal apical fibrosis. Note the nodular density near the left hilum suggestive of a new growth. (Courtesy of Dr. Paul A. Bishop.)

side. There was no evidence of bronchiectasis. All the sputum examinations were negative for tubercle bacilli.

It was thought that the source of hemoptysis was probably from the area of red-dened bronchial mucosa opposite the old tuberculous lesion, presumably from a ruptured bronchial vessel. This patient returned to work within two weeks after the cessation of hemoptysis. There has been no indication of relapse of tuberculosis.

Case 3. A 60 year old housewife had had minimal pulmonary tuberculosis years ago, but had remained symptom-free until September, 1953, when she developed cough, expectoration, shortness of breath and hemoptysis. The chest roentgenogram (figure 3) showed healed tuberculous lesions in the left upper lobe, with density in the lower third of the right lung suggestive of an acute pneumonic process, possibly tuberculous in nature. Repeated sputum examinations, as well as the study of the bronchial secretions, were negative for tubercle bacilli and malignant cells. The

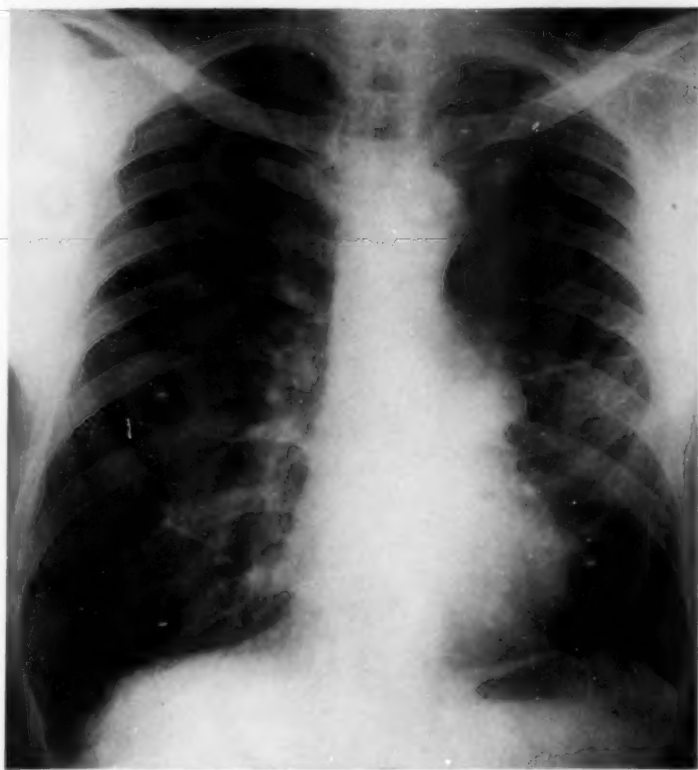


FIG. 2. Near the left hilum there is a calcified area with diffuse fibrosis in the lower half of the left lung.

hemoptysis continued, with gradually worsening uremia. The autopsy showed pneumonitis in the right lower lobe and pronounced nephrosclerosis. The lesion in the left upper lobe was well healed tuberculosis.

The hemoptysis in this patient was unquestionably from the area of pneumonitis.

Case 4. A 35 year old man developed a tuberculous cavity in the right upper lobe in 1941 (figure 4). In 1942 thoracoplasty was performed on the right side.

Between 1943 and 1952 his tuberculosis was considered inactive. In May, 1953, he developed considerable dyspnea, cough, and expectoration with hemoptysis. The roentgenogram (figure 5) suggested diffuse pleuritis over the left lung, with a small nodular density just above the diaphragm. One day while being studied in a hospital the patient died quite suddenly of respiratory failure. The autopsy showed that the original cavity in the right lung, although flattened, was still present. Its wall was red, without exudate. Both the smears and the cultures of the material from the

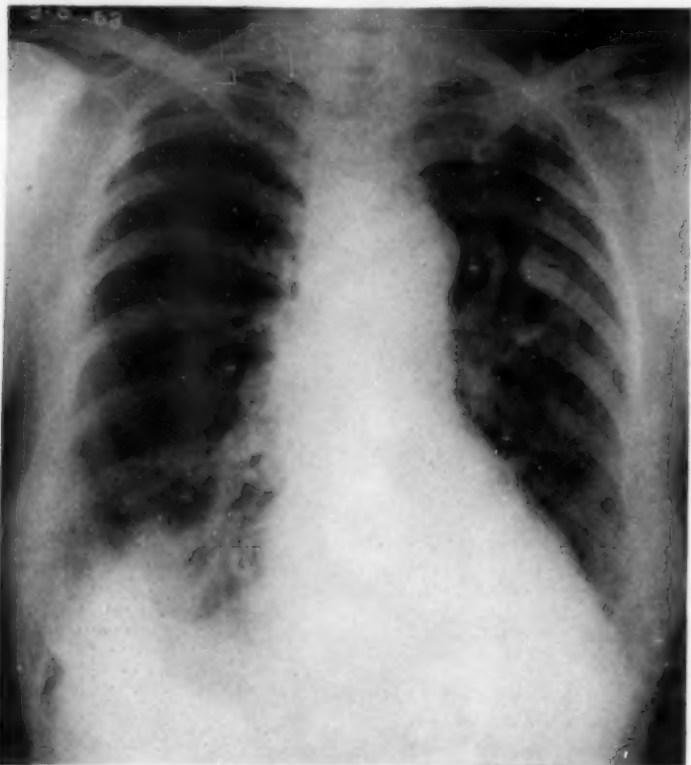


FIG. 3. There is a dense nodular shadow in the left upper hemithorax. In the right base is a dense shadow suggesting pneumonia. (Courtesy of Dr. Paul A. Bishop.)

cavity failed to show tubercle bacilli. Nontuberculous pneumonia with minute cavities was found in the left lower lobe. There was nothing to indicate active pulmonary tuberculosis in either lung. It was presumed the hemoptysis had originated in the pneumonic area.

It was interesting to note that, despite the collapse for 10 years, the cavity in the right upper lobe persisted although flattened and devoid of

tubercle bacilli. Subsequent to thoracoplasty on the right side, artificial pneumothorax was instituted and maintained for four years on the left side because of scattered tubercles. Over the years there had been slow progression of pleuritis on the left side, causing gradually worsening respiratory insufficiency.

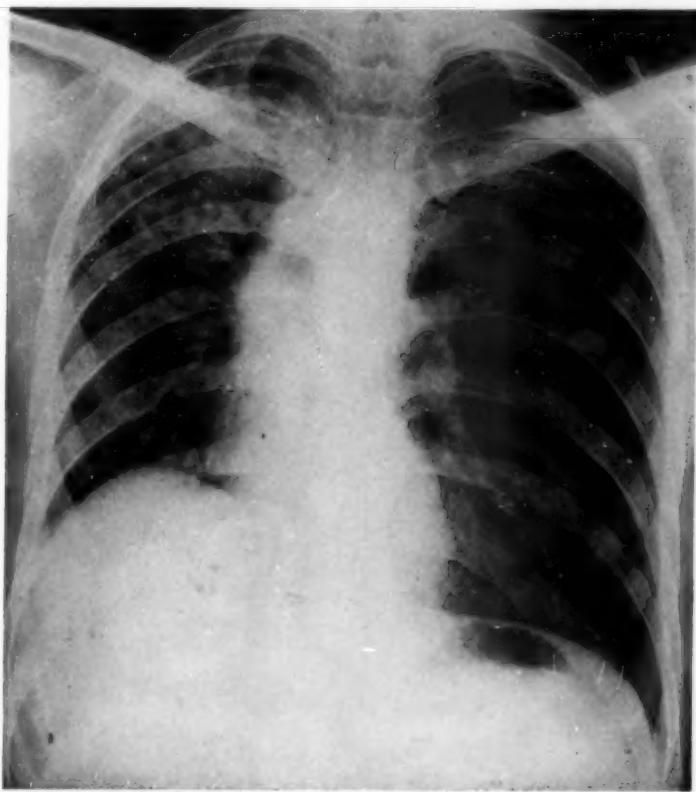


FIG. 4. There is a cavity in the right upper lobe with scattered tubercles.

Case 5. A 45 year old housewife developed pulmonary tuberculosis in the left lung in 1939, for which artificial pneumothorax was instituted. The pulmonary tuberculosis subsided and she remained symptom-free until 1945, at which time she had two attacks of hemoptysis. The chest roentgenogram indicated complete atelectasis of the left lung. A bronchoscopic examination revealed an ulcer in the left main bronchus. Both the culture of the secretions and the examination of the granulation tissue from the ulcer failed to show tubercle bacilli. She has been well for the past eight years.

This patient illustrates hemoptysis in inactive tuberculosis, presumably from a bronchial ulcer of undetermined cause.

Case 6. A 50 year old man had been treated for moderately advanced tuberculosis with bed-rest and chemotherapy in 1946. Following this treatment he became entirely symptom-free until 1949, when he developed cough, expectoration and



FIG. 5. The left lung is now smaller. There is diffuse pleuritis over the left lung. The left half of the diaphragm is elevated and its outer portion is adherent to the chest wall.

hemoptysis. It was thought that he had a relapse of pulmonary tuberculosis, but repeated examinations of the sputum were negative for tubercle bacilli. The chest roentgenogram (figure 6) showed residual tissue changes in the upper portions of the lung field resulting from tuberculosis. In addition, about the left hilum there was some haziness which was interpreted to be a new tuberculous process. The bronchoscopic examination showed a mass in the left bronchus which, on histologic examination, proved to be bronchogenic carcinoma.

In this patient tuberculosis and bronchogenic carcinoma coexisted. It has been suggested that tuberculosis may be one of the causes of bronchogenic carcinoma. This is not likely, since the incidence of bronchogenic carcinoma in tuberculous patients is no greater than that in the general population.

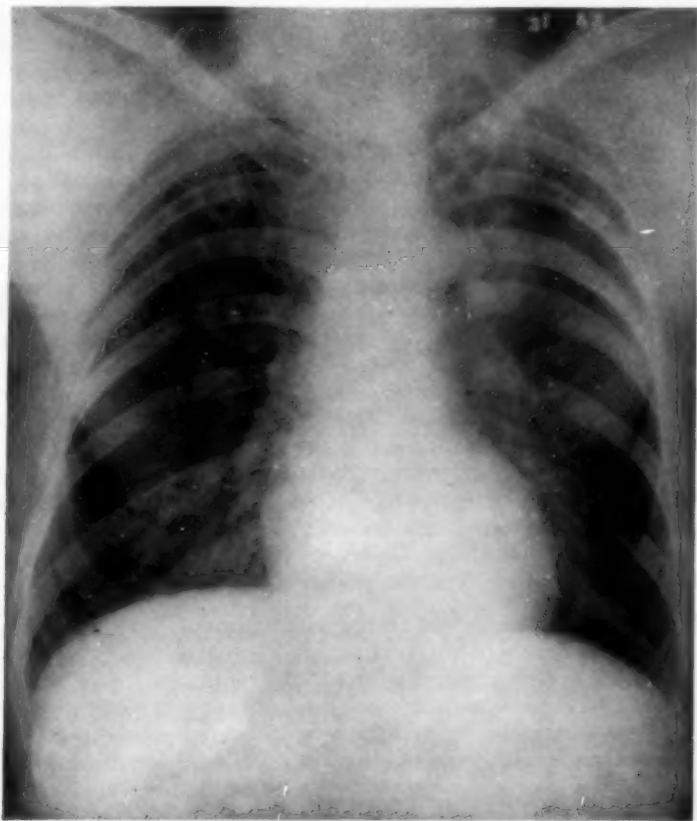


FIG. 6. In the apical areas there are strandlike shadows. At the left hilum there is haziness suggesting carcinoma.

COMMENT

This study suggests that hemoptysis in individuals having apparently inactive pulmonary tuberculosis does not mean relapse of pulmonary tuberculosis except in rare instances. In the majority of patients it was not possible to explain the cause of hemoptysis. The attacks were not in any

way related to exertion, to the menstrual cycle, or to acute respiratory infections. Nevertheless, this symptom should be regarded as potentially dangerous; it is wise for the patient to remain in bed while studies are carried out. The material brought up should be examined by smear, culture, and inoculation for tubercle bacilli. Roentgenograms of the chest will be useful. If the sputum is negative, bronchoscopic examination may be carried out even in the presence of active hemorrhage. The bronchial secretions should be examined for tubercle bacilli as well as for cancer cells. When all examinations are negative and the patient in the week or two following the cessation of the hemorrhage has shown no constitutional reaction, his return to normal activity is permissible.

In a given patient the amount of hemorrhage may help in deciding whether the patient has carcinoma, bronchiectasis or tuberculosis. In bronchogenic carcinoma the amount of blood brought up by the patient is usually small. As a rule the patient brings up blood-streaked or blood-tinged sputum without frank hemorrhage. In pulmonary tuberculosis and bronchiectasis, on the other hand, the amount of blood brought up may be massive. It has been suggested by Sokoloff¹ that, when a person with arrested pulmonary tuberculosis develops hemoptysis, bronchiectasis or varicosity of the bronchial blood vessels within the fibrotic lesions may be considered. In patients with what appears to be a single massive pulmonary hemorrhage, if the bronchial lumens are clear and show no signs of recent hemorrhage on bronchoscopic examination, O'Keefe² suggests examination of the esophagus for bleeding. At times it may be difficult for the patient to be certain whether the bleeding was from the lungs or the gastrointestinal tract, particularly if the hemorrhage causes choking.

SUMMARY

1. Twenty-one patients out of 123 with apparently inactive pulmonary tuberculosis had attacks of hemoptysis.
2. The hemoptysis signified relapse of the tuberculosis in only three.
3. In 13 the cause of the pulmonary hemorrhage could not be determined.
4. In the others, the hemorrhage was due to pneumonia, pneumonitis, new growth, and nontuberculous lesions in the bronchial mucosa.
5. In instances of hemoptysis, unexplained after careful study, it seems safe to permit asymptomatic patients to resume usual activity within a week or two after the cessation of the pulmonary hemorrhage.

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TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS *

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SUBACUTE bacterial endocarditis has been treated with reasonable success for nine years. The number of recoveries from this formerly universally fatal infection is a most gratifying experience in medicine and the therapeutic achievement is attributable directly to the antimicrobial efficacy of penicillin. In general, most studies indicate that approximately 70 per cent of all patients treated for the infection recover, although there is a considerable discrepancy in mortality rates among individual reports.¹⁻⁵ One perplexing feature of specific antimicrobial treatment, quite apparent lately, is the lack of a recent decrease in the mortality rate from the 30 per cent to 35 per cent first recorded in 1945 and 1946.^{1,2} This report, by describing the course and therapy of 48 consecutive cases of subacute bacterial endocarditis, attempts both to explain failures of treatment and to suggest methods of overcoming the causes of some of them.

THE PATIENTS ‡

Forty-eight patients, ages 15 to 78 years, were treated for subacute bacterial endocarditis from January, 1948, through August, 1952 (table 1). There were 17 females and 31 males. All were patients on the combined medical services of the Syracuse Medical Center Hospitals. All were seen by at least one of the authors during the course of the infection, the outline of therapy was suggested by that observer, and each patient received approximately the same accessory nursing and medical attention. All bacteriologic work was performed in the Syracuse City Laboratory,§ and tests of sensitivity to various antimicrobial agents were performed in the laboratories of the Department of Medicine.

Infecting microorganisms were isolated from 38 of the 48 patients during life. The diagnosis in four additional patients was made secure by autopsy or operative findings (table 2). No organisms were recovered at any time from six of the 48 patients (12.5 per cent). In each of these six

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† With the technical assistance of Leonard Canarilli.

‡ Permission to use private patients in this series was granted by Dr. E. C. Reifstein, Dr. F. Geiger, Dr. J. G. F. Hiss, Dr. W. Pennock, Dr. R. D. Johnson, Dr. S. T. Killian, Dr. J. D. Ayer, Dr. G. B. Andrews, Dr. H. A. Feldman, Dr. E. G. Allen and Dr. J. J. Hogan.

§ Under the direction of Dr. O. D. Chapman.

TABLE I
Age of Patients with Subacute Bacterial Endocarditis

Age	Male	Female	Number Recovered
15*	0	1	0
20-29	4	4	5
30-39	6	2	6
Subtotal	17 (35%)		11 (65%)
40-49	6	3	7
50-59*	3	2	3
60-69	8	3	8
70+*	4	2	4
Subtotal	31 (65%)		22 (71%)
Total	31	17	33 (69%)

* One patient in each of these groups was undertreated with penicillin.

individuals the history, clinical findings and course of the disease were such that the diagnosis seems unquestionable.

Sensitivity of 35 of the causative bacteria to various antimicrobial agents was determined (table 2). Three of 26 isolated strains of *Streptococcus viridans* were resistant to more than 1.2 units penicillin/ml. of serum. All seven enterococci were resistant to more than 1.5 units of penicillin (the greatest resistance was 5 units). The single beta hemolytic streptococcus was sensitive to penicillin (less than 1 unit of penicillin per milliliter). The paracolon aerogenes was initially sensitive to both chloramphenicol and streptomycin, but prior to the patient's death they became totally resistant to at least six different antimicrobial agents as well as to various combinations of these. Thus, 10 of the 35 causative gram-positive organisms (29

TABLE II
Causative Organisms in 48 Cases of Subacute Bacterial Endocarditis

Organisms	Number of Patients	Total Number of Patients Cured	Number of Patients with Organisms Resistant to Penicillin (More than 1.5 u/c.c.)	Number of Patients Cured with Resistant or Untested Organisms
Alpha Streptococci	26	21	3	2
Alpha Streptococci	3	1	Sensitivities not done	1
Enterococci	7	3		4
Beta Streptococci	1	1		—
Paracolon Aerogenes	1	0	1	0
Organisms Not Isolated	10*	7†	—	—
Total	48	33	11	7

* Three of these died. At autopsy all had active subacute bacterial endocarditis; no organisms were cultured, although bacteria were seen in microscopic sections of the valves.

† One of these proved to have subacute bacterial endocarditis at time of elective mitral valvulotomy. Remaining six patients in the group were diagnosed upon clinical grounds alone. Each had clear-cut cardinal symptoms of the disease.

per cent) were resistant to between 1.5 and 5 units of penicillin, and the gram-negative organism became resistant to all antibacterial agents (total resistant group, 32 per cent).

Thirty-six of the 48 patients had rheumatic heart disease and 10 had other forms of valvular heart disease (table 3). The two other patients

TABLE III
Type of Heart Disease and Outcome of Therapy in 48 Cases
of Subacute Bacterial Endocarditis

Number of Patients		Rheumatic Heart Disease			Arteriosclerotic and Other Forms of Valvular Heart Disease			Congenital Heart Disease
		Aortic	Mitral	Both	Aortic	Mitral	Both	
Living	33	3	13	9	3	2	2	1
Dead	15	3	3	5	1	—	2	1
Total	48	6	16	14	4	2	4	2*

* Both with patent ductus arteriosus, one proved at autopsy.

presumably had congenital defects of the heart or great vessels but only one, a patent ductus arteriosus, was proved at autopsy. Twenty-eight of the 48 patients had aortic valvular disease; in 18 it was combined with mitral stenosis, and in the other 10 aortic insufficiency alone was present. Sixteen patients had mitral stenosis. Heart failure was observed before or during treatment in 25 cases, but in only seven was it a serious complication.

TABLE IV
Therapy with Penicillin in 48 Cases of Subacute Bacterial Endocarditis

	Number of Patients	Daily Dose Penicillin in Millions of Units		Duration of Therapy in Days Average and Range	
		Approximate Average Daily Dose	Range	Living	Dead
Sensitive Organisms	24	1-2.	0.7-12.	31 (20-52)	48 (45-52)
Resistant Organisms	11	15 [*]	2.4-36.	52 (28-66)	26 (6-150)
Unknown	13	4.6	0.5-12	41 (19-62)	31 (8-68)

* One patient received no penicillin.

Therapy was instituted in each patient as soon as the diagnosis was established, either by the finding of microorganisms in the circulating blood, or after an interval of from three to 14 days' observation in the hospital during which period fever, heart murmur, hematuria and other evidences of embolization confirmed the diagnosis. Penicillin was the basic therapeutic substance (table 4). Prior to the determination of sensitivities to antibacterial agents, a regimen utilizing approximately 1,000,000 units of peni-

cillin daily in divided doses of 100,000 units every two or three hours was administered to most. Adjustment of dosage of penicillin was accomplished after the sensitivities were measured, or, lacking these, when the clinical course indicated necessary changes. In the single case caused by a gram-negative organism penicillin was not used. He received in succession a variety of chemotherapeutic agents alone and in combination, streptomycin and chloramphenicol being the major ones.

Treatment was continued in most for a minimum of three weeks after evidences of active infection had subsided or until death (table 4). Among the 33 survivors there were two who received only 20 days' continuous therapy, four others who received treatment for from 21 to 27 days, and three whose therapy was extended for more than 50 days (52, 62 and 66 days, respectively). The average therapeutic course in those who survived was 34 days. Two of the 15 patients who died received only six and eight days of treatment. Therapy was continued to death in all of the others and extended for from 28 to 150 days.

THE RESULTS OF THERAPY

Thirty-three of the 48 patients survived the infection, and 15 died. Among the 48 there were three whose first infection was adequately controlled but who, after from three to 10 months, had an infectious relapse and retreatment was required. All recovered again (table 5). During the interval between infections two were in reasonably normal health; the other perhaps had never completely recovered from the first infection, although his clinical remission seemed adequate at the time. He received only 14 days of therapy for the primary disease, and 36 for the relapse commencing 14 weeks later.

The Dead: Fifteen patients died during therapy for subacute bacterial endocarditis (figure 6). Death in nine was abrupt, and in six there was gradual deterioration in health, with either irreversible heart or kidney failure. Perforation or rupture of an aortic valve cusp occurred in six patients. Other immediate and associated causes of death are listed in table 6. No autopsies were performed upon five patients. In two whose death was abrupt, aortic valvular disease existed at the time of death. Although bacteriologic cure had been achieved in some, 14 of the 15 deaths were attributed directly to the infection, and in the 10 who were autopsied there was decisive evidence of this. One individual died from hemorrhage apparently arising in a bronchial vessel immediately following an operative attempt to close a patent ductus arteriosus. Though the patient was in clinical remission at the time of operation, autopsy showed the vegetative disease to be still active.

The Living: Thirty-three patients survived and are living three to 59 months after completion of therapy for subacute bacterial endocarditis. All patients with mitral stenosis alone have had apparent complete recovery from

TABLE V
Three Relapses Following Initial Clinical Remission among 48 Cases of Subacute Bacterial Endocarditis

Causative Organism	1st Infection Total Penicillin Dose in Millions of Units	Approximate Daily Dose in Millions of Units	Days of Rx.	Change in Symptoms and Signs during 1st Rx.	Symptoms and Signs during Interval	Duration of Remission	2nd Infection Total Penicillin Dose in Millions of Units	Approximate Daily Dose in Millions of Units	Days of Rx.	Result
No organism found	30	1.8	14	Improved markedly. Afebrile and compensated	Fever, transient chest pain and minor emboli	3½ mo.	54	1.5	36	Cure
No organism found	264	9	42	Improved, had occasional spike of fever, no emboli	Gradual relapse with new emboli, petechiae and fever	9 mo.	72	12	6	Cure with subsequent valvulotomy
Alpha strep. (3 u/c.c.),	63.8	1.6	45	Improved, no evidence SBE. Remained on prophylactic Aureomycin for 5 mo.	Gradual relapse 4 mo. after cessation of prophylaxis period with increased heart failure, fever to 101° and petechiae	10 mo.	252	12 + 2 gm. Chloromycetin for 10 days	21	Cure*

* Patient remained on prophylactic Aureomycin, 1 gm. daily for approximately 9 months after second infection, with remission persisting, and cure seems secure 1.5 years later. Organism with second attack serologically identical with that found in first infection.

the infection, and there has been no further gross deterioration in cardiac function as a result of the superimposed infection. In general, the patients with aortic insufficiency who recovered have been less capable of returning to their former work, and at least two of them have remained in cardiac failure, not present prior to the complicating infection. Only one patient was given an antimicrobial agent over a long period for prophylactic reasons (table 5). The others have been treated on the occurrence of an intercurrent respiratory infection, and all have received short-term prophylactic treatment with penicillin for traumatic events of any type.

Age of the patient did not play a significant rôle in the percentage of recoveries. Of the 17 patients with the disease under the age of 40, 11 (65 per cent) survived (table 1). Twenty-two of the 31 patients over 40 lived, and of the 17 over 60 years 12 (70 per cent) recovered. The oldest patient in the series (78 years) died, but there were two survivors over the age of 75 and four over 70. Sex did not alter the outcome (table 6). Seventeen of the 48 patients were female (34 per cent), and five of the 15 deaths were women (33 per cent).

CAUSES OF FAILURE OF TREATMENT

In the management of most bacterial diseases, a certain number of patients die despite adequate antimicrobial therapy. In the majority of infections, acute or chronic, caused by organisms susceptible to one or more of the easily available agents, the mortality figure approaches 5 per cent, but in some, particularly chronic infections, the rates are higher. This is evident in the therapy of subacute bacterial endocarditis. Generally, in the case of the patient who is given adequate therapy but who dies, the cause of death is explained by the host's inability to form sufficient body defenses, or because these have been depleted, or because for some unexplained reason the defenses are inadequate and do not aid the host effectively in eradicating the infectious agent, or frequently because the inflammatory changes associated with the invasion preclude return to adequate function of an essential tissue. All reasons for the 30 per cent or 35 per cent mortality rate associated with the therapy of subacute bacterial endocarditis are not, however, so easily elucidated, although certain of the failures are clearly explainable.

Deaths in the present series can be divided into those which in retrospect were preventable and those which were not. Three patients received inadequate antimicrobial therapy, and the infectious part of their disease was not, therefore, controlled. This was evident at autopsy in two (table 6). Dosage of penicillin given each was not arranged properly and too little concern was paid to the partial resistance of the causative organisms to penicillin. Inadequate therapy in the third patient is perhaps understandable, if not excusable, because organisms were not cultured during his life and treatment could be prescribed only arbitrarily. These three deaths may be considered preventable. With their exclusion it is difficult indeed to

estimate, even with hindsight, how the remaining 12 patients might have been saved with a different therapeutic regimen. Six deaths were directly attributable to mechanical changes in circulation, incompatible with living. Two others died suddenly, presumably from acute vascular accidents in the heart or head. Three had uncontrollable congestive heart failure and received standard and enthusiastic treatment for it, and the infection in the twelfth individual was caused by organisms completely resistant to all antimicrobial agents then in common use.

TABLE VI
Causes of Death in 15 Patients with Subacute Bacterial Endocarditis

Organisms	Age	Sex	Type of Heart Disease	Duration of Therapy	Immediate Cause of Death	Associated Causes of Death
Sensitive to Penicillin	66	M	RHD: AS, ? MS	33	Active aortic vegetations, rupture aneurysm sinus	Active rheumatic carditis, congestive heart failure, cirrhosis
	42*	M	HRD: AI	53	Perforation aortic valve cusp	Moderate heart failure
	75†	F	RHD: MS	35	Congestive heart failure	Probable active carditis
	30*	M	RHD: AI & MS	45	Rupture aortic valve cusp	Severe myocarditis
	22*‡	M	RHD: AI & MS	46	Cerebral vascular accident‡	Mild heart failure
Resistant to Penicillin	78†	F	ASHD: AS, MI	37	Uremia‡	—
	59‡	M	HRD: AI	28	Acute progressive heart failure‡	—
	47*	M	ASHD: AI, AS	6	Rupture aortic valve cusp	Nephritis, CNS emboli
	50*†	F	RHD: AI, MS	32	Mesenteric thrombosis with peritonitis	Renal infarcts, active vegetation
	23*	M	Patent ductus arteriosus	150	Postoperative hemorrhage	Active vegetation
No Organisms Cultured during Life	60	F	RHD: MS	8	Congestive heart failure	Rupture chordae tendineae, nephritis, myocarditis
	15†	F	RHD: MS	20	Toxemia of chronic infarction, organisms found at autopsy	Active vegetation, myocarditis, renal infarcts
	38*	M	RHD: AI	66	Rupture aortic valve cusp, organisms found at autopsy	Myocarditis, nephritis, mycotic aneurysm
	60*	M	RHD: AI & MS	68	Rupture aortic valve cusp, organisms found at autopsy	Nephritis, CNS emboli
	26*‡	M	RHD: AI & MS	20	Sudden death—cause unknown‡	Heart failure

* Death abrupt.

† These patients were probably undertreated with penicillin.

‡ No autopsy.

This last patient is a noteworthy example of a generally accepted thesis about therapeutic failures in this infection, to which we cannot and do not subscribe. It is not evident, in this series at least, that increased numbers of organisms completely resistant to penicillin explain to any degree the lack of improvement of the mortality figures since 1945.^{6,7} It may be true that more cases of subacute bacterial endocarditis are now being caused by organisms partially resistant to penicillin than in 1945, but this event by itself does not reduce chances for survival, and actually there are no data here or in the literature to substantiate the idea. Instances of fecal or viridans strains of streptococci resistant to more than 1.5 units of penicillin oc-

curred in 28 per cent of this group, but their presence did not preclude successful therapy. For example, five of 10 patients died who were infected with penicillin-resistant organisms, but two of the five were grossly undertreated because the level of susceptibility was ignored or was not recognized (table 6). It may be surmised that with proper therapy one or both might have recovered, changing the mortality rate in this group to approximately that in the other categories. In only rare instances are the causative organisms totally resistant to penicillin or streptomycin, or to a combination of one or both of them with other available antimicrobial agents.

Furthermore, other features of the disease commonly reported to explain unsuccessful treatment played no important rôle in the outcome in this series.^{4,8} Age and sex had no decisive influence upon the survival, even though the age of the patients as a whole has changed significantly in the past decade. Blumer, for example, has stated that approximately 90 per

TABLE VII
Time of Institution of Therapy in 48 Patients with Subacute Bacterial Endocarditis

	Living		Dead	
	Duration 1st Symptoms before Hospitalization (days)	Delay of Therapy after Hospitalization (Days)	Duration 1st Symptoms before Hospitalization (days)	Delay of Therapy after Hospitalization (days)
Patients with sensitive organisms (24)	10 to 150, average 56	1 to 14, average 3.3	14 to 180+, average 90+	1 to 7, average 3.3
Patients with resistant organisms (11)	30 to 180, average 103	1 to 7, average 3.5	15 to 180, average 87	1 to 2
Patients with organisms not cultured during life (13)	7 to 200, average 107	1 to 14, average 4.5	60 to 180, average 92	1 to 4, average 2.8

cent of all cases occur before the age of 40 years.⁹ In the present series over 65 per cent of the patients were 40 or over. Despite the implication that recovery might be expected less often because of older age, this is not so. Promptness in diagnosis and the early establishment of specific therapy were not directly related to the results. Ten of the 15 who died were treated within 60 days of the first symptom (table 7), as well as could be determined historically. Because of the insidiousness of the infection and the failure of the patient to recognize promptly the development of endocarditis, early diagnosis is difficult, and it is therefore impossible to suggest how much better the results might have been had the patients presented themselves for therapy earlier. The general health of the patients who succumbed similarly could not be regarded as inferior to that of those who recovered. Although it would be convenient to believe that heart failure, impaired renal function, fever and other evidences of chronic toxicity from infection might conceivably reduce the effectiveness of the host's body defenses to the disease, a comparison of the health of those who died and of

those who recovered revealed no impressive differences. The patient with the worst degree of heart failure recovered, the youngest and clinically the healthiest patient in the group died after only two months of illness. Although a significant degree of heart failure was present in six of the 15 patients who died, it was also evident in 19 of those who recovered. These examples serve only to point up the problem of suggesting that deteriorating health, from either the preëxisting heart disease or the infection *per se*, can be used as a reasonable explanation for the high mortality rates in treated cases of subacute bacterial endocarditis.

The one unavoidable conclusion which can be drawn from the present series is that patients with aortic valvular disease fared far worse than those with mitral or congenital defects. This was true both in the incidence of death and in the failure to return to previous health in those who survived. No precise explanation can be given, nor is there an easy answer to altering this unfortunate observation. It is possibly true that as vegetations upon the aortic valve heal, there results a significant weakening of valve cusps due to fibrosis, and with this a loss of adequate tensile strength. The rupture or perforation of the aortic cusp apparently bears no relationship to the size of the heart, presence of heart failure, duration of the valvular lesion or duration of the superimposed infection.

The causes of therapeutic failure, to summarize, are clearcut but are not always avoidable. The age and sex of patient, type of organic heart disease, general health of patient, promptness or delay in diagnosis and institution of specific antimicrobial therapy play no important rôle in determining outcome. Organisms totally resistant to penicillin occur occasionally, and a significant number of patients are undertreated because causative organisms are partially resistant to penicillin, but neither of these events explains satisfactorily the 30 per cent to 35 per cent mortality rate. Fatal accidents due to the loss of integrity of the aortic cusps and the major vessels in the heart and central nervous system account for a large proportion of the deaths, but methods to avert them are not apparent. It is interesting to note, though, that paradoxically many are probably the result of successful antibacterial therapy. With subsidence of the infection, healing of the aortic valve occurs by fibrosis and apparently either the resultant scar is not sufficiently strong or the insufficiency is increased.

DISCUSSION

With these data and observations it is possible to outline a therapeutic regimen for subacute bacterial endocarditis in general terms, although it must be emphasized that each patient presents his own individual problem and no single design can suffice for all cases.

The patient with subacute bacterial endocarditis cannot or does not defend himself well with either humoral or cellular defenses, as evidenced by the outcome in the untreated disease. If therapeutic success is to be

achieved, treatment with antimicrobial agents must accomplish a unique thing in the host, the almost total eradication of the infecting microorganisms without appreciable help from the host. Therefore, any therapeutic weapon must have certain characteristics: It must be bactericidal, capable of killing the vast majority of the causative organisms, its administration over a long period of time must not be associated with important side effects, and it must penetrate clots. Aureomycin, chloramphenicol, Terramycin and the sulfonamides fail to fulfill these criteria for effectiveness, and must consequently be labeled as inferior drugs in the treatment of subacute bacterial endocarditis.^{4, 7, 20} Bacitracin and polymyxin-B have been used too infrequently to determine their efficacy. Only penicillin and streptomycin, singly or in combinations, fulfill the necessary requisites, and clinical experience has proved this well. The sole design for a therapeutic program with either of these two drugs is so to administer them that concentrations in the serum and within the vegetations are attained which are higher than the sensitivity of the organisms as measured *in vitro*. Further, it must be so prescribed that these concentrations are maintained for sufficiently long periods of time to assure penetration into and at the base of the avascular vegetations, at which area the organisms are lodged. For penicillin-susceptible organisms, i.e., susceptible at levels less than 1 unit, approximately 1,000,000 units penicillin are required per day, divided into eight to 12 parenteral injections. If the organisms are susceptible to less than 0.1 unit, lesser amounts of penicillin are needed, but no less than 500,000 units penicillin per day should ever be prescribed. Insoluble preparations of penicillin are also never indicated. It is probably not necessary to combine streptomycin with the penicillin for the therapy of infections caused by susceptible organisms.

Vastly greater daily amounts of penicillin are required for patients whose endocarditis is caused by organisms resistant to more than one unit of penicillin per milliliter. Because the material is so very nontoxic, the upper limit of daily dosage need not be defined. In the present series 36,000,000 units were given to one patient for 27 days without event. However, as Robbins and Tompsett and others have pointed out,^{6, 11} there can be no question that streptomycin must be added to massive therapy with penicillin to secure best results in infections caused by relatively resistant organisms. One to 2 gm. of streptomycin daily, plus large amounts of penicillin (5,000,000 to 20,000,000 units), may act in synergism against the organism. Because partially resistant organisms occur in approximately 30 per cent of all cases with subacute bacterial endocarditis, the combined penicillin-streptomycin regimen is commonly used.

Two methods are utilized to avoid the necessity of administering penicillin by the intermittent intramuscular route in those patients requiring large doses. Two to 4 gm. of Benemid daily by mouth delay the urinary excretion of penicillin and thus enhance blood levels. With its use, lesser amounts of penicillin may be needed. An easier method of administering

large amounts of penicillin is by the use of a constant intramuscular or deep subcutaneous drip. The daily dose of penicillin is dissolved in a small (250 to 500 c.c.) amount of saline or in 5 per cent glucose solution and the clysis allowed to drip slowly and evenly throughout the required period. No complications with this method of administration have been encountered, and resultant blood levels are more reasonably constant than those following an intravenous drip.

The total daily amount of penicillin required to maintain adequate concentrations of the agent at the site of the infection is not difficult to determine. With the knowledge of the sensitivity of the organism *in vitro*, the height of the required blood level can be estimated and the proper dosage prescribed. Periodic determinations of the blood level determine whether the dosage is adequate or needs adjustment. Direct measurement of the antibacterial potency of the patient's blood serum against the causative microorganisms is another method to determine that the dosage of drug is proper.¹²

During the three to six day period between the time the diagnosis is suspected and cultures are taken and the time when reports of the sensitivity are available for interpretation, it is our recent custom to start the patient on a regimen of penicillin utilizing 12,000,000 units daily. Proper adjustment is made only after the report of the laboratory observations is completed.

Antimicrobial therapy must be continued for a minimum of three weeks after subsidence of evidences of active infection. The type of inflammation, the location of the organisms within the vegetation, the sluggishness of response of the bacteria, and the lack of response of the host all require a long exposure of the organisms to the drug to assure a satisfactory, nonrelapsing arrest of the infection.

Accessory therapeutic measures include those agents which are needed in any individual with acute infection and with heart disease. Their prescription needs little description. Although anticoagulants have been used by some in the therapy of endocarditis,¹³ they are neither indicated nor necessary, and, indeed, may be contraindicated.

With adequate specific antimicrobial therapy the patients with subacute bacterial endocarditis respond in an impressive manner. Blood cultures become cleared of organisms within 24 hours, and the temperature becomes normal (commonly by the fourth day, less often after longer periods). Small showers of emboli (petechiae) may continue for 10 days to two weeks, and major emboli can occur during the first week, but are uncommon thereafter. Abnormal urinary findings are observed for from two to three weeks, with only a gradual diminution in the number of red blood cells, casts and albumin. Mitral murmurs do not change appreciably during the uncomplicated healing phase of disease, although during the first week they may become less shrill, less high-pitched and, as the heart slows with improve-

ment, less intense. Aortic murmurs more commonly change in characteristics. Some become extraordinarily loud and harsh. Heart failure, which is frequently observed early in the course of the infection in the older patients, does not respond promptly or well to diuresis and digitalization, although it is relieved as the infection subsides. Rarely does a patient remain in failure after cure. Tachycardia may persist for more than two weeks in most, probably because of the myocarditis accompanying the disease.

In the patient who is not treated successfully the course of the disease varies, depending upon the reason for the failure. With a totally resistant organism the infection continues according to the descriptions of the past, with inevitable death in from three to five months from one or more of the usual complications.⁹ With inadequate antimicrobial therapy, there may be a subtly dangerous and misleading remission which may appear initially like cure. This is particularly evident in patients who are being treated solely with Aureomycin, chloramphenicol or Terramycin. Actually, with these agents the inevitable relapse often occurs only after cessation of treatment, and the relapse is prompt in most. It must be emphasized again that, as is true with many other infections, insufficient therapy may lead to a clinical remission which is rarely maintained.

Complications during unsuccessful therapy and causes of death differ little from those formerly observed. Nonspecific diffuse myocarditis, focal or diffuse nonspecific glomerulonephritis alone or in combination, serious vascular accident in a major vessel such as a ruptured mycotic aneurysm or major embolic phenomena, all occur unless antimicrobial treatment reverses the invasiveness and extension of the vegetative endocardial or valvular lesion.

The patient who is cured of subacute bacterial endocarditis usually has either minor or no long-term sequelae from the infection or its treatment. Two events alter this general statement. If heart failure develops after treatment has been well established and after the infectious part of the disease has been controlled, the chances for permanent improvement in cardiac function are reduced appreciably. This can also be predicted roentgenographically: if the enlarged heart, so commonly seen early in the disease, does not return toward normal during treatment, it will probably never do so. Therefore, the assessment of the size of the heart at the end of treatment is important for prognosis.⁸

The opportunity to develop a second or multiple episodes of subacute bacterial endocarditis is not altered by a first infection. If the patient remains free of the disease for 12 months following cessation of specific antimicrobial therapy, a subsequent bout of subacute bacterial endocarditis is presumably a re-infection and not an infectious relapse. Because it is not the purpose of this review to discuss prophylaxis, only one statement need be made about preventing subacute bacterial endocarditis. In any individual with heart disease penicillin should be administered prophylactically prior

to any manipulative procedure, either medical or dental. The dose and the duration of this protection need not be excessive, e.g., two daily doses of 300,000 units of procaine penicillin on the day of and the day after the trauma are generally sufficient.

SUMMARY

The treatment of subacute bacterial endocarditis has been reviewed. Thirty-three of 48 patients with this proved cardiac infection survived and 15 died (31 per cent). Causative microorganisms were not recovered during life from 10 patients (21 per cent). Organisms resistant to more than 1.5 units penicillin per milliliter were present in 11 patients, and in one of these the organism became insensitive to all antibacterial agents. Forty-seven of the 48 patients were treated with penicillin, although 16 received streptomycin in addition and four were given other adjuvant antimicrobial agents. The one who received no penicillin was treated with streptomycin, Terramycin, chloramphenicol, Aureomycin and sulfonamides, alone or in combination. The dosage of penicillin or streptomycin was almost totally dependent upon the measured sensitivity of the causative microorganism. The therapeutic regimen was designed according to this level, and it was necessary to use excessive amounts of both agents in cases in whom the level of resistance to penicillin was of a high order. The duration of specific antimicrobial therapy extended in most for more than 21 days after cessation of all evidence of active infection. Accessory therapy was prescribed as indicated.

This therapeutic regimen is therefore recommended for most cases of subacute bacterial endocarditis. Two thirds or more of the patients should recover if the program is wisely designed and administered. The reasons for unsuccessful management are discussed: resistant and untreatable infecting microorganisms, insufficient antimicrobial therapy, irreversible heart failure, and the other causes of death which have been so well described in the past. Specific antimicrobial therapy cannot be expected to alter the anatomical changes or complications resulting from the inflammation caused by the offending microorganisms. Its sole usefulness is to eradicate the organisms which stimulate the pathologic alterations prior to the advent of the complication, thus reducing the chance for their occurrence. Early diagnosis and institution of proper therapy thus are essential. The single striking exception to the general reasons for failure is the occurrence of perforation or rupture of the aortic valve, which occurred and caused death in six of the 15 patients in this series. This observation has not been emphasized in the past, and no preventative measures can be proffered to avoid its occurrence in the future.

The prognosis of patients cured of subacute bacterial endocarditis is good for long-term health. Patients with aortic insufficiency and those in heart failure after successful antimicrobial therapy are the exceptions to this.

Reinfection is possible. Subacute bacterial endocarditis, despite the overall efficacy of wisely administered powerful antimicrobial agents, continues to be a serious and difficult infection to treat, and the results of therapy for it have not appreciably improved in the past five years.

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THE INORGANIC ELEMENT CONTENT OF CERTAIN HUMAN TISSUES*

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THE purpose of this paper is threefold: first, to point out the average content of certain inorganic elements in human tissues by the study of material from 910 autopsied patients; second, to suggest that some, if not all, of these elements may be micronutrients which play a rôle in the enzyme systems of the body; and third, to determine whether the mercurial diuretics are harmful to the human kidney.

Although the rôles of certain inorganic elements in the enzyme systems of the body—iron, for example—are understood fairly well, the functions of other metals have remained relatively obscure. Even when only rough estimates could be made of the amounts of inorganic elements present in the tissues, the observation that concentrations of these inorganic elements varied in particular disease states suggested the possibility that disordered metabolism of some mineral or minerals normally present in the body might account for at least a fraction of the observed findings. With the development of precise instruments for the determination of metallic content in the various tissues and body fluids, it now becomes possible to study these relationships. It is important that we discover which of the inorganic elements are micronutrients, and what part, if any, each trace metal plays in the enzyme systems of the body. The competition between one element and another for enzyme systems, such as that between molybdenum and copper in "peat scours" disease, is thought-provoking.

NEED FOR STANDARD DATA

Before we can judge whether the amount of a particular metal present in an organ is excessive, "normal" or unusually low, we first must establish standards.

Most studies reported in the literature have been designed to gauge the applicability to biologic material of spectrographic and other precise methods of measuring the metallic content of organs. Consequently, these former investigations usually have been done on but a few patients, with emphasis placed on technic rather than on the establishment of tables for comparative purposes. The population examined in this study is sufficiently large to furnish us with the needed standard data.

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THERAPEUTIC IMPLICATIONS

As clinicians, we have a further cause for interest in the metallic content of vital organs and its import. For many years we have administered metallic compounds to our patients as therapeutic measures. Now we have at hand a means for assaying the cumulative effects of these compounds, and it is important that we know to what extent these metals are assimilated

TABLE I
Copper
Mg. per 100 grams dry tissue*
(Cases without cirrhosis of liver)

	Ages											Totals above 1 Year
	0- 3 Mo.	3 Mo.- 1 Yr.	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-	
Liver	32.49	2.35	2.36	3.31	2.66	2.48	3.04	2.82	3.07	2.52	2.64	2.76
S.E.	1.91		0.20	0.76	0.57	0.37	0.38	0.22	0.22	0.21	0.26	0.10
N.	67	3	16	4	7	9	14	35	49	43	22	199
Kidney	2.63	0.84	1.31	1.46	1.25	1.61	2.28	2.11	1.80	1.57	1.79	1.77
S.E.	0.34		0.21	0.26	0.25	0.40	0.45	0.26	0.18	0.14	0.28	0.09
N.	67	3	16	4	7	9	14	37	50	43	21	201
Heart	2.35	—	1.61	1.59	1.53	1.42	1.84	1.54	1.93	1.93	2.22	1.83
S.E.	0.27		0.23	0.09	0.30	0.33	0.24	0.14	0.18	0.23	0.36	0.09
N.	21		12	3	6	4	10	23	37	24	18	137
Brain	1.23	—	1.44	1.86	1.41	2.21	1.79	2.29	2.43	2.12	1.81	2.07
S.E.	0.16		0.13	0.07	0.33			0.24	0.55	0.15	0.31	0.16
N.	10		7	4	3	3	3	12	19	15	9	75
Lung	0.98	—	0.69	0.97	1.40	1.24	1.45	1.11	1.37	1.26	1.27	1.21
S.E.	0.21		0.07	0.18				0.13	0.19	0.16	0.27	0.08
N.	6		6	4	2	3	3	12	18	15	9	72
Spleen	3.06	—	0.56	0.73	0.44	2.47	3.66	0.82	1.06	0.74	1.00	1.03
S.E.	1.45		0.11	0.23				0.17	0.20	0.06	0.23	0.15
N.	8		7	4	2	3	3	12	19	14	9	73

* Average Values.

S.E.—Standard Error.

N.—Number of Cases.

This table is included in the paper by Drs. Butt, Nusbaum, Gilmour and DiDio in the March, 1954, issue of the *American Journal of Clinical Pathology* (their Table IV).

and stored by and eliminated from the body. What permanent effects, if any, follow prolonged administration of particular metallic compounds? Do these permanent alterations in metallic concentration outweigh in importance the benefits conferred by administration of the therapeutic compounds? These are important questions which must be answered. As a cardiologist, G. C. G. has been interested particularly in the effects of orally and parenterally administered mercuric compounds in the management of congestive heart failure.

SCOPE OF THE STUDY

We have been interested in determining the amounts of six inorganic elements—copper, iron, lead, manganese, mercury and zinc—in various tissues of the body. Furthermore, we have gone on to analyze the cumulative effects of one element—mercury—as used in the management of congestive heart failure.

TABLE II
Iron
Mg. per 100 grams dry tissue*

	Ages											Totals above 1 Year
	0- 3 Mo.	3 Mo.- 1 Yr.	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-	
Liver	89.84	24.62	35.15	53.50	25.66	37.53	42.64	54.55	45.79	47.72	63.02	47.66
S.E.	5.54	7.14	6.75	17.82	4.83	5.13	6.30	6.39	3.15	4.66	6.96	2.11
N.	68	5	13	4	10	15	17	46	57	52	25	239
Kidney	38.84	19.88	23.38	41.25	20.45	24.82	30.30	27.43	26.68	29.18	27.26	27.38
S.E.	6.85	2.00	2.85	7.32	3.25	2.14	4.57	1.57	1.41	2.40	1.30	0.84
N.	67	5	13	4	10	15	17	48	58	54	25	244
Heart	30.00	17.03	17.28	26.77	13.33	19.81	27.30	26.04	22.23	23.95	25.95	23.39
S.E.	3.26		1.51	4.98	2.00	2.13	6.47	3.43	1.11	1.82	2.13	0.99
N.	21	3	8		8	7	11	30	43	31	20	162
Brain	19.19	7.67	15.77	17.45	17.00	22.12	32.10	20.50	21.19	19.83	18.70	20.47
S.E.	1.82			1.49	3.81	2.16	16.37	1.69	1.87	0.95	1.71	0.99
N.	10	3	3	4	4	5	4	14	22	20	10	86
Lung	98.63	45.57	40.33	56.45	46.25	90.90	76.35	157.00	122.29	100.74	71.43	103.34
S.E.	19.89			20.72	5.17	23.21	26.70	27.53	22.62	8.68	7.06	8.49
N.	8	3	3	4	4	5	4	14	21	21	10	86
Spleen	59.28	38.33	51.00	42.93	72.75	93.60	55.00	114.11	154.22	115.10	104.53	112.45
S.E.	15.77				29.64	22.05		26.37	36.03	15.52	17.27	9.97
N.	7	3	3	3	4	5	3	14	22	21	10	85

* Average Values.

S.E.—Standard Error.

N.—Number of Cases.

This table is included in the paper by Drs. Butt, Nusbaum, Gilmour and DiDio in the March, 1954, issue of the *American Journal of Clinical Pathology* (their Table VI).

METHOD OF STUDY

Concentrations of copper, iron, lead, manganese, mercury, zinc and molybdenum present in the brain, heart, lung, spleen, kidney and liver were determined by chemical or spectrographic analysis from material taken at autopsy from organs of 910 patients studied at the Los Angeles County Hospital. Portions of the thoracic and abdominal aorta were also analyzed for the presence of a single element—lead. No attempt was made to study separately the concentrations in the three coats of the aorta.

Material from 410 cases was subjected to chemical analysis. In 500 additional cases the emission spectrograph was employed to determine the concentrations of metals in the tissues.

All elements emit characteristic radiations when they are excited sufficiently by a source of energy, either thermal or electrical. The spectrograph is utilized to characterize and measure amounts of radiation emitted by the specific elements. In this study, ashed samples of the organs to be studied were placed in solution within graphite electrodes and subsequently volatilized into the arc stream during the burning of the arc. Radiation given off by the individual metallic elements was then sorted out by the spectroscope into line spectra according to the individual wave lengths, measured, and recorded on film. A detailed discussion of the method of analysis employed has recently been published by Butt et al.¹

METALLIC CONTENT

Concentrations of five metallic elements present in the tissues are itemized in table 1 (copper), table 2 (iron), table 3 (lead), table 4 (manganese)

TABLE III
Lead
Mg. per 100 grams dry tissue*

	Ages											Totals
	0-3 Mo.	3 Mo.-1 Yr.	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-	
Liver	0.358	0.457	0.553	0.364	0.482	0.514	0.600	0.669	0.551	0.557	0.486	0.517
S.E.	0.027	0.094	0.049	0.152	0.071	0.084	0.086	0.055	0.044	0.059	0.064	0.019
N.	67	6	13	4	10	15	16	46	57	54	25	313
Kidney	0.296	0.294	0.450	0.206	0.449	0.357	0.593	0.423	0.346	0.332	0.333	0.362
S.E.	0.036	0.120	0.070	0.010	0.098	0.043	0.098	0.042	0.031	0.024	0.074	0.015
N.	67	6	13	4	10	15	17	47	58	53	25	315
Heart	0.240	0.159	0.171	0.078	0.113	0.256	0.212	0.212	0.216	0.147	0.191	0.195
S.E.	0.053		0.052	0.019	0.027	0.068	0.036	0.038	0.040	0.022	0.034	0.014
N.	20	3	8	4	8	7	11	31	43	31	20	186
Brain	0.072	0.151	0.068	0.055	0.108	0.099	0.046	0.071	0.092	0.092	0.053	0.082
S.E.	0.013			0.016	0.056	0.029		0.013	0.017	0.018	0.006	0.007
N.	9	3	3	4	4	5	3	14	22	20	10	97
Lung	0.162	0.173	0.118	0.154	0.193	0.135	0.229	0.253	0.289	0.256	0.255	0.234
S.E.	0.031			0.022	0.038	0.091	0.089	0.038	0.031	0.038	0.047	0.015
N.	7	3	3	4	4	5	4	14	21	21	10	96
Spleen	0.115	0.105	0.121	0.195	0.189	0.175	0.188	0.189	0.559	0.263	0.181	0.275
S.E.	0.021			0.115	0.055	0.068		0.036	0.162	0.035	0.023	0.041
N.	8	3	3	4	4	4	3	14	22	21	10	97

* Average Values.

S.E.—Standard Error.

N.—Number of Cases.

This table is included in the paper by Drs. Butt, Nusbaum, Gilmour and DiDio in the March, 1954, issue of the *American Journal of Clinical Pathology* (their Table VIII).

TABLE IV
Manganese
Mg. per 100 grams dry tissue*

	Ages											Totals
	0-3 Mo.	3 Mo.-1 Yr.	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-	
Liver	0.459	0.608	0.665	0.456	0.466	0.507	0.596	0.546	0.616	0.484	0.572	0.532
S.E.	0.026	0.121	0.084	0.120	0.047	0.055	0.076	0.042	0.040	0.025	0.038	0.015
N.	68	6	13	4	10	15	17	46	57	54	25	315
Kidney	0.267	0.295	0.387	0.417	0.324	0.317	0.366	0.311	0.303	0.291	0.272	0.301
S.E.	0.017	0.046	0.034	0.095	0.029	0.040	0.045	0.018	0.015	0.018	0.017	0.007
N.	67	6	13	4	10	14	17	48	58	54	25	316
Heart	0.161	0.150	0.137	0.113	0.118	0.118	0.126	0.148	0.172	0.130	0.153	0.147
S.E.	0.012		0.020	0.001	0.017	0.017	0.012	0.028	0.024	0.008	0.022	0.008
N.	21	3	8	4	8	7	11	30	43	31	20	186
Brain	0.139	0.149	0.113	0.118	0.186	0.144	0.128	0.139	0.126	0.127	0.117	0.132
S.E.	0.012			0.017	0.037	0.017	0.001	0.012	0.007	0.007	0.009	0.003
N.	10	3	3	4	4	5	4	14	22	20	10	99
Lung	0.301	0.108	0.084	0.130	0.149	0.156	0.133	0.175	0.169	0.199	0.162	0.177
S.E.	0.096			0.016	0.029	0.035	0.001	0.017	0.016	0.030	0.023	0.012
N.	8	3	3	4	4	5	4	14	21	21	10	97
Spleen	0.121	0.098	0.089	0.113	0.179	0.098	0.222	0.136	0.152	0.128	0.122	0.135
S.E.	0.011			0.017	0.059	0.030	0.023	0.013	0.024	0.009	0.011	0.008
N.	8	3	3	4	4	5	4	14	22	21	10	98

* Average Values.

S.E.—Standard Error.

N.—Number of Cases.

This table is included in the paper by Drs. Butt, Nusbaum, Gilmour and DiDio in the March, 1954, issue of the *American Journal of Clinical Pathology* (their Table VII).

and table 5 (zinc). Amounts present are expressed in milligrams per 100 gm. of dry tissue. Significant shifts in concentration with age will be discussed separately for each metal.

Copper: Material from persons with cirrhosis of the liver was deemed unsuitable for inclusion in a table of normal values because hepatic copper storage is very erratic in this disease. The principal site of copper storage is the liver. Analysis of non-cirrhotic cases shows large amounts of copper in the livers of the newborn (roughly 12 times that found in adults and older children), and copper values above those for adults are yielded by the infant kidney, heart and spleen. Copper is found to be greatly increased in premature infants and in infants with congenital malformations of the heart incompatible with life.

Iron: High iron values in the liver at birth are seen to drop precipitously in the following months. Generally elevated values in the infant remain at a somewhat lower level throughout later childhood and middle life until, in the later years, the onset of congestive failure is accompanied by a marked rise in iron content of the spleen, lung and, to some extent, the liver.

Lead: Lead was present in comparatively small amounts in all organs studied. Study of the aortas of 25 persons showed that, although the lead content of the abdominal segment averaged only 0.397 mg. per 100 gm. of dry tissue before the age of 40, it increased to an average concentration of 0.686 mg. per 100 gm. after 40. Lead in the thoracic segment increased from an average value of 0.486 mg. per 100 gm. of dry tissue in persons under 40 to 0.634 mg. per 100 gm. in persons over 40. Apparently a relatively constant amount of lead is present up to the age of 40, after which lead content increases from 50 to 100 per cent, depending upon the amount of arteriosclerosis present.

Manganese: Quantities of manganese remain relatively constant throughout the life span, save for a somewhat elevated amount in lung tissue at birth.

Zinc: Zinc is more prevalent in the liver and lung of the premature infant and the mature infant under three months of age than in the older child or the adult.

TABLE V
Zinc
Mg. per 100 grams dry tissue*

	Ages											Totals above 1 Year
	0- 3 Mo.	3 Mo.- 1 Yr.	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-	
Liver	41.80	14.98	18.14	22.28	20.72	15.48	23.06	21.30	22.56	22.07	26.73	21.92
S.E.	2.70	2.13	1.14	6.62	0.95	1.65	3.22	1.46	1.36	1.48	2.67	0.70
N.	68	6	13	4	10	15	17	46	57	54	25	241
Kidney	19.47	11.09	15.73	16.48	14.49	15.52	22.66	19.31	21.13	17.93	19.73	19.04
S.E.	1.48	1.36	1.31	2.31	0.93	1.18	3.55	1.15	1.86	0.99	1.35	0.64
N.	66	6	13	4	10	15	17	48	38	54	25	244
Heart	15.60	11.00	11.76	9.90	9.88	12.08	11.40	11.42	12.17	12.08	12.80	11.85
S.E.	1.37		0.74	0.91	0.88	1.05	0.97	0.39	0.78	1.12	1.70	0.39
N.	21	3	8	4	8	7	11	30	44	31	20	163
Brain	6.47	4.77	4.82	4.78	6.47	5.04	3.81	4.45	5.51	4.68	4.77	4.93
S.E.	0.63			0.66	0.73	0.23	1.08	0.41	0.59	0.26	0.55	0.21
N.	10	3	3	4	3	5	4	13	22	20	10	84
Lung	24.58	7.40	6.63	8.59	8.85	8.16	7.86	8.41	9.29	8.19	9.43	8.63
S.E.	9.23			1.02	1.72	0.56	1.20	0.76	1.02	0.55	1.69	0.39
N.	8	3	3	4	4	5	4	14	22	20	10	86
Spleen	8.71	6.95	5.90	8.15	10.92	10.46	10.48	7.99	7.47	8.62	10.07	8.57
S.E.	2.09			1.32	2.12	2.77	2.54	0.60	0.52	0.55	1.70	0.38
N.	8	3	3	4	4	5	4	13	23	21	10	87

* Average Values.

S.E.—Standard Error.

N.—Number of Cases.

This table is included in the paper by Drs. Butt, Nusbaum, Gilmour and DiDio in the March, 1954, issue of the *American Journal of Clinical Pathology* (their Table V).

TABLE VI
Inorganic Micronutrients—Liver
Mg./100 grams of dry tissue*

	Premature to 3 Mo.	3 Months to 1 Year	1 Year to 100 Years
Copper	32.49 \pm 1.91	2.35	2.76 \pm 0.10
No.	67	3	199
Zinc	41.8 \pm 2.7	14.98 \pm 2.13	21.92 \pm 0.70
No.	68	6	241
Iron	89.84 \pm 5.54	24.62 \pm 7.14	47.66 \pm 2.11
No.	68	5	239
Manganese	0.459 \pm 0.026	0.608 \pm 0.121	0.532 \pm 0.015

* Average Values—Standard Error.
No.—No. of Cases.

Copper, zinc, iron and manganese are all known to be essential for proper fetal development. In table 6, the amounts of these micronutrients commonly present (a) from birth to the third month of life, (b) from three months to one year of age, and (c) from one year on are compared, in order to contrast the sizable metallic requirements of the developing fetus with the lesser amounts needed in extra-uterine life.

MERCURY

The organs of 45 patients with congestive heart failure were studied to determine (1) whether mercury is normally present in the human body; (2) whether the administration of mercuric compounds as a therapeutic measure would result in the cumulation of additional stores of mercury in the body, and (3) what damage, if any, results from the continued administration of mercuric compounds. As mercury exerts its effects mainly on the kidney, any damage which might occur would presumably be reflected in an elevated nonprotein nitrogen level.

Of the group studied, 15 patients had no record of having received mercury. Chemical analysis of their kidneys, livers and spleens revealed an average content of 2.05 mg. mercury in the kidney, 0.37 mg. mercury in the liver, and 0.12 mg. mercury in the spleen per 100 gm. of dry tissue. As both young and old individuals were included in this group, we may assume that a trace of mercury may be found in the tissues at all ages.

Fourteen persons had received 400 mg. or less of mercury. This had raised the average mercuric content of the kidney somewhat, to 2.96 mg. per 100 gm. of dry tissue. Hepatic content remained virtually unchanged, and there had been a slight drop in the average mercuric content of the spleen.

Sixteen patients had received a minimum of 400 mg. of mercury, which had been administered either orally or parenterally over periods ranging from three weeks to 40 months. The average dose received by members of this group was in the neighborhood of 4,692 mg. of mercury. The sub-

stantial amounts of mercury these patients had received had raised the average mercuric content of the kidney to 15.29 mg. per 100 gm. of dry tissue, the average content in the liver to 1.38 mg., and the average content in the spleen to 0.32 mg. The heart was found to contain an average of 0.27 mg. of mercury and the lungs 1.27 mg. Amounts of residual mercury in the kidney, liver and spleen may be compared in table 7.

TABLE VII
Mercury Content in 45 Cases

	Average Content—Mg. per 100 Grams Dried Tissue		
	Kidney	Liver	Spleen
No mercury given	2.05	.37	.12
Given 400 Mg. Hg or less	2.96	.34	.04
Given 400 Mg. Hg or more*	15.29	1.38	.32

* Average, 4,692 mg. Hg.

As can be seen from table 8, the three groups were roughly comparable from the standpoint of associated kidney disorders.

Did the cumulative amounts of mercury exert a noxious effect? Any damage to the kidney presumably would be reflected in the nonprotein nitrogen level of the blood. Nonprotein nitrogen values were available for only four of the 15 patients who had received no mercury. One of the four had very marked uremia, which made the average nonprotein nitrogen

TABLE VIII
Kidney Disease in 45 Cases

	15 Cases No Hg	14 Cases 400 Mg. Hg or Less	16 Cases 400 Mg. Hg or More
Nephrosis	2	2	2
Infarct of kidney	1	0	2
Pyelonephritis	0	1	2
Nephrosclerosis	6	6	5
Hydronephrosis	0	0	1
No disease	6	5	4

value for the group spuriously high—122 mg. per 100 c.c. The average nonprotein nitrogen value for the patients who had received 400 mg. mercury or less was 66 mg. per 100 c.c. The average nonprotein nitrogen value for the group who had received an average of 4,692 mg. of mercury was 73 mg. per 100 c.c. The nonprotein nitrogen values could not be interpreted as indicating that the larger amounts of mercury in the tissues were harmful.

SUMMARY

We have presented tables showing the average content of copper, iron, lead, manganese, mercury and zinc in tissues obtained from 910 autopsied patients. These values serve as standards for further study. The rôle of the inorganic elements as micronutrients is briefly suggested.

Copper is present in abnormally large amounts in premature infants, and especially in infants with congenital cardiovascular anomalies. Iron is high in the tissues of the newborn, then drops to a constant level until the later decades of life, when the content again reaches the levels found in the newborn. Lead is found in constant amounts in all tissues at all ages, but in the aorta after the age of 40 years the content increases 50 to 100 per cent concomitant with the degree of arteriosclerosis present, compelling the speculation that lead, calcium and perhaps other inorganic elements compete for the rôle of catalyst in the enzyme metabolism in the aorta. Manganese and zinc are present in constant amounts in all tissues. Mercury—an immediate problem because of its widespread therapeutic usage—is found in the tissues of all patients not known to have received mercuric compounds. Small and massive doses are not injurious to the kidney in the absence of anuria due to hyponatremia.

Persons interested in a review of spectrographic methods now in use may wish to consult the excellent article by Smith and associates.² A second article by the same authors covers the applicability of spectrographic methods to medical problems.³

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THE HEART IN ACUTE GLOMERULONEPHRITIS *

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INTRODUCTION

ACUTE glomerulonephritis is a disease with an unknown etiology whose immediate clinical course has been well described. Since the classic description by Blackall¹ in 1813 and Bright² in 1827, continuous investigation has immeasurably enlarged our knowledge of the disease.

The incidence of involvement of other organs, however, is still widely disputed. One of the most disputed points is the incidence of cardiac involvement in acute glomerulonephritis. It was this facet of the problem that initiated the present study.

Goodhart,³ in 1879, is generally credited with recognizing and describing cardiac failure in acute nephritis. Since that time numerous reports have dealt with the clinical and electrocardiographic manifestations, with conflicting opinions on the incidence. Murphy⁴ reports cardiac insufficiency in 17 per cent of 94 cases; Marcolongo,⁵ in 40 per cent of 80 cases; Ellis,⁶ in 20 per cent of 100 cases; Master and associates,⁷ in 33 per cent of 24 cases; Rubin and Rapoport,⁸ in 25 per cent of 55 cases; and Whitehill and associates,⁹ in 71 per cent of 138 cases.

The pattern of acute glomerulonephritis lends itself naturally to conflicting reports by various authors, as the changes witnessed in the disease are so transitory. This report is a study of 88 cases of acute glomerulonephritis at Milwaukee County Hospital. The clinical features were classified into the five cardinal syndromes of glomerulonephritis. The occurrence of the syndromes was as follows:

TABLE I
Occurrence of Syndromes

	No.	Per Cent
Urinary syndrome	88	100.0
Edema	73	82.9
Hypertension	68	77.3
Azotemia	66	73.0
Uremia	—	—
Genuine	—	—
Convulsive	16	18.1

In acute glomerulonephritis cardiac enlargement and other cardiac changes, although present on the patient's admission, may regress so rapidly that the changes pass unobserved or prove of little significance when dis-

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covered. The same is true of electrocardiographic abnormalities. Often, too, observers focus complete attention on edema and kidney involvement, overlooking for the most part typical symptoms of tachycardia, dilated cervical veins and dyspnea.

The reported incidence of heart failure in acute nephritis is determined not only by the severity of nephritis but also by careful and early clinical examinations. The interest of the observers is most important in early and correct diagnosis. However, it is not only the incidence of cardiac involvement that is significant; rather, it is the presence of heart failure as well as the rapidity of the development of the cardiac changes that is of importance.

Cardiac involvement was believed to be present if any one or combination of the following criteria occurred: (1) the presence of clinical heart failure; (2) cardiac changes on x-ray examination, and (3) electrocardiographic abnormalities.

Special note of the relationship of convulsions to heart failure will be made.

THE PRESENCE OF CLINICAL HEART FAILURE IN ACUTE GLOMERULONEPHRITIS

The etiology of the heart failure which occurs in acute nephritis is not established, although such authors as Volhard¹⁰ and LaDue¹¹ believe that hypertension is the precipitating cause. Volhard¹⁰ believed the injury was caused by hypertension and that edema protected the heart. LaDue,¹¹ in a study of 12 patients all of whom had right heart failure, as indicated in every instance by an elevated venous pressure with cardiac dilatation, believed that systemic hypertension was the initiating cause and that the right heart failure was secondary to the left heart failure. He felt there was a close correlation between the decrease in the systemic blood pressure and the disappearance of the signs of congestive heart failure.

On the other hand, Davies,¹² in a study of five cases of acute glomerulonephritis by venous catheterization, found cardiac output normal and believed there was no evidence for the incrimination of hypertension in the heart failure. He reported that dyspnea was or may be absent, that cardiac output and circulation times were within normal limits, and that the heart rate was normal or even slow in the presence of raised venous pressure. He also stated that the correlation between hypertension and venous congestion was poor, and that a fall of venous pressure and disappearance of edema may precede the fall of systemic blood pressure. It must be pointed out, however, that in measuring cardiac output, right auricular blood is not a true "mixed venous sample," as is pulmonary artery blood. In two of the five cases the mean right ventricular pressures were measured and samples may have been taken from the right ventricle to calculate cardiac output. This is still not so satisfactory as pulmonary artery samples are.

Gore and Saphir¹³ studied the hearts of 160 patients with acute

glomerulonephritis. It was their opinion that myocarditis may be a factor in the cardiac insufficiency of acute glomerulonephritis. Changes suggestive of myocarditis were found in 16 of the 160 cases. It was their impression that these myocardial changes are of such a patchy distribution that they probably are easily overlooked and this may explain the low incidence of 10 per cent in this study.

In the present report the clinical diagnosis of cardiac failure was established by three methods: (1) a clinical diagnosis of heart failure with an adequate description of dyspnea, orthopnea, dilated neck veins, pulmonary râles, palpable liver, or any combination of these findings; (2) an adequate description of the typical findings of cardiac insufficiency, as mentioned above, without a specific diagnosis of heart failure; and (3) postmortem findings of pulmonary edema, passive congestion of the liver, or similar pathologic characteristics of heart failure. The possibility that a massive pleural effusion might give rise to the symptoms described in points one and two was considered but this was not present in any of the cases. A diagnosis of cardiac failure was established in 22 of the 88 cases, as follows:

TABLE II
Incidence of Cardiac Failure

	No.	Per Cent
Clinical heart failure	8	9.0
Evidence of heart failure from chart review	13	14.9
Post mortem	1	1.0
Total	22	24.9

Cardiac failure was diagnosed more commonly in patients over 21, occurring in 10 out of the 22 cases (45.5 per cent). In contrast to this, failure under 21 years of age occurred in 12 out of 66 cases (18.2 per cent). The ratio of age to diagnosis was as follows:

TABLE III
Relation of Age to Cardiac Failure

Age by Decade	Total Study	Cardiac Failure	Per Cent
0-10	29	5	17.8
11-20	37	7	18.9
21-30	12	5	41.6
31-up	10	5	50.0
Total	88	22	

Dean¹⁴ has pointed out the lack of correlation between evidence of cardiac damage and high blood pressure. Such observations have been reported by others.^{9, 15} Murphy, Grill and Moxon¹⁶ also reported a case of heart failure and death in a patient who had no rise of blood pressure.

In this series, in contrast to others, a close association between severe hypertension and cardiac failure was found. We used the classification of normal, moderate and severe. A normal blood pressure in the cases under 16 was any with a systolic pressure under 140 mm. of mercury and a diastolic of under 85 mm. of mercury. This is admittedly a little high. In the age group from 16 to 40, a normal blood pressure was defined as any pressure 140/90 mm. of Hg or under. Over 40 years of age, any pressure under 150/100 mm. of Hg was considered normal.

A case was classified as moderate hypertension if the blood pressure was above the normal for the age but the diastolic pressure was beneath 110. Any patient, regardless of age, whose diastolic pressure was over 110 fell into the severe classification.

Cardiac failure was more frequent in patients with moderate or severe hypertension, as follows:

TABLE IV
Relation of Hypertension to Cardiac Failure

Hypertension	Total Study	Per Cent	Cardiac Failure	Per Cent
Normal	20	22.7	1*	4.5
Moderate	37	42.0	10	45.4
Severe	31	35.2	11	50.0
Total	88	99.9	22	99.9

* Patient had had convulsion 12 hours prior to admission to hospital, so hypertension most probably was present at that time. All blood pressures in the hospital were normal.

Clinical heart failure was present in 18 of the 22 patients on admission to the hospital. Failure disappeared upon bed-rest and proper administration of fluids. In all cases improvement was accompanied by a fall in blood pressure. In four of the patients, cardiac failure occurred in the hospital. In one, injudicious administration of fluids in the treatment of anuria probably contributed to fatal heart failure. In the remaining three, the initial part of the hospital course was uncomplicated. Then infection (pre-antibiotics) resulted in an exacerbation of the nephritis, with an increase in the severity of the urinary picture, sudden elevation of the blood pressure and convulsions. Heart failure followed with dramatic suddenness.

The failure present appeared to be primarily left-sided in type, with right-sided failure later. All the patients manifested dyspnea; occasionally it was present only on exertion, but in the majority it was present at rest. In none of the patients was a pure right-sided heart failure noted. Venous pressure and circulation time were measured in such a small number of patients that no conclusions could be drawn. Two of the patients manifested a gallop rhythm, and one had a tic toc rhythm.

Although cardiac failure occurred in the group as a whole in only 25 per cent of the cases, it occurred in nine of the 18 patients who had convulsions.

CARDIAC CHANGES ON X-RAY EXAMINATION

There is no more acceptable evidence of cardiac involvement than the demonstration of enlargement by roentgenogram. Teleroentgenograms were available in 29 of the 88 cases of nephritis. The results were as follows:

TABLE V
Teleroentgenograms in 29 Cases of Acute Nephritis

	No.	Per Cent
Normal	12	41.4
Cardiac enlargement associated with	17	58.6
a) Pulmonary congestion	10	34.5
b) Bilateral pleural effusion	3	10.3
c) Right pleural effusion alone	2	6.9
d) Left pleural effusion alone	0	—

Since height and weight were not recorded in all instances and there is no reliable method for comparison of a so-called "normal" in children,¹⁷ only clinical judgment of the teleroentgenograms was used to determine cardiac enlargement.

In eight of the patients serial measurements of the cardiac area were made. The method used was that of Bardeen,¹⁸ in which the superior and inferior cardiac borders were delineated by arbitrary lines constructed by continuation of the profile of the right and left cardiac margins as seen in the six foot teleroentgenograms. Within this area there is the heart proper and a small portion of the cardiac extremity of the pulmonary artery and aorta. A small portion of the left auricle may be cut by the line that curves toward the right from the left border, but this is insignificant. This delineated area may be measured by planimetry.

This method is most satisfactory for serial cardiac area measurements, since it tends to minimize the error of different levels of the diaphragm on serial roentgenograms.¹⁹ Three determinations were done on each roentgenogram, with agreement within 1 per cent. A factor of 5 per cent was used to correct for the magnification occurring in the six foot teleroentgenogram.²⁰

Since we were most interested in serial changes in the size of the heart, the "normal" for each patient was the lowest cardiac area observed in the serial x-rays. In the majority of cases this was the last film. It is possible in some of the cases that if more x-rays had been taken further changes would have been noted. However, this would lead to an underestimation of cardiac enlargement in the present study and would not affect the final conclusions. A correlation of these various factors is given in the accompanying table.

In cases 1, 2 and 7, the maximal decrease in size occurred within the first week. For the most part the first roentgenogram was taken within

a few days of admission, with the exception of case 2, in which it was taken 12 days after admission. These rapid changes in cardiac size would have been overlooked if the first films had been taken 10 days to two weeks after admission.

ELECTROCARDIOGRAPHIC ABNORMALITIES

The incidence of electrocardiographic changes is of importance only as a reflection of the frequency of cardiac involvement. The possible mechanisms which may be responsible for or may contribute to the electrocardiographic changes are hypertension, alterations in the blood volume, electrolyte changes, or toxic changes. Myocarditis has been implicated by Gore and Saphir.¹⁸

TABLE VI
Correlation of Changes in Heart Size to Blood Pressure, Heart Failure
and Electrocardiogram

Case No.	Age	Date of X-ray	Heart Failure	Corrected Planimetry (sq. cm.)	Blood Pressure	Enlargement (%)	EKG
1. D. A.	6	7/28/40	Yes	85.5	122/78	42.9	8/1/40 Abnormal
		8/3/40		74.1	94/40	23	
		8/11/40		59.9	90/45	0	
2. B. B.	12	5/11/41	No	131.5	164/114	54.2	5/19 Normal
		5/17/41		104.5	155/110	23.5	5/13 Normal
		8/21/41		90.6	128/92	5	
		9/11/41		84.6	120/80	0	
3. N. C.	13	3/9/45	No	119.3	156/110	39	3/9 Abnormal
		9/5/45		85.8	120/78	0	4/13 Normal
4. N. L.	15	9/1/44	No	190	130/80	39	9/2 Abnormal
		9/13/44		153.9	130/90	0	(Only I)
5. D. P.	6	9/9/42	No	72.2	120/78	27.3	9/7 Normal
		10/23/42		56.7	104/52	0	(Only I)
6. D. M.	9	3/11/41	No	57.5		15.1	Normal
		3/12/41		66.3		0	
7. D. W.	19	4/1/49	No	134.0	158/110	35.6	Abnormal
		4/7/49		116.8	134/80	18.2	Abnormal
		4/13/49		100.2	130/80	1.3	Borderline
		4/21/49		98.8	140/90	0	Normal
		4/29/49		103.5	150/90	4.7	Normal
		6/1/49		96.8	128/78	-2.0	Normal
		7/28/49		98.9		0	Normal
		9/6/49		98.8	120/58	0	Normal
		1/12/50		94.0		-4.8	—
		11/3/51		102.6	145/80	+3.8	—
		11/19/53		104.2	160/95	+5.5	—
8. G. M.	30	1/31/53	Yes	121.2	160/100	24.7	Normal
		2/10/53		120.9	120/80	24.4	Normal
		3/13/53		97.2	130/80	0	—
		10/21/53		103.5	120/80	6.5	Normal

Of the 88 cases studied, 47 had electrocardiograms. The electrocardiograms fell into the following groups:

TABLE VII
Incidence of Electrocardiographic Abnormalities

EKG	No.	Per Cent	Average
Normal	26	55.3	1.65
Borderline	1	2.1	2.00
Abnormal	20	42.6	2.75

Any of the changes which were considered pathologic and placed an electrocardiogram in the abnormal group were found on the first tracing (with the exception of three). Follow-up tracings to note the disappearance of the abnormalities accounted for the higher average of roentgenograms in the abnormal group.

As has been previously reported by Langendorf and Pick,²¹ LaDue and Ashman²² and Ash et al.,²³ the abnormalities most frequently noted were in the T wave changes in Lead I, which were either of low voltage or inverted. This was also true of this series. The Q-T and P-R interval was calculated from the tables of Ashman and Hull.²⁴ In this series of cases, electrocardiographic abnormalities occurred as illustrated in the following table:

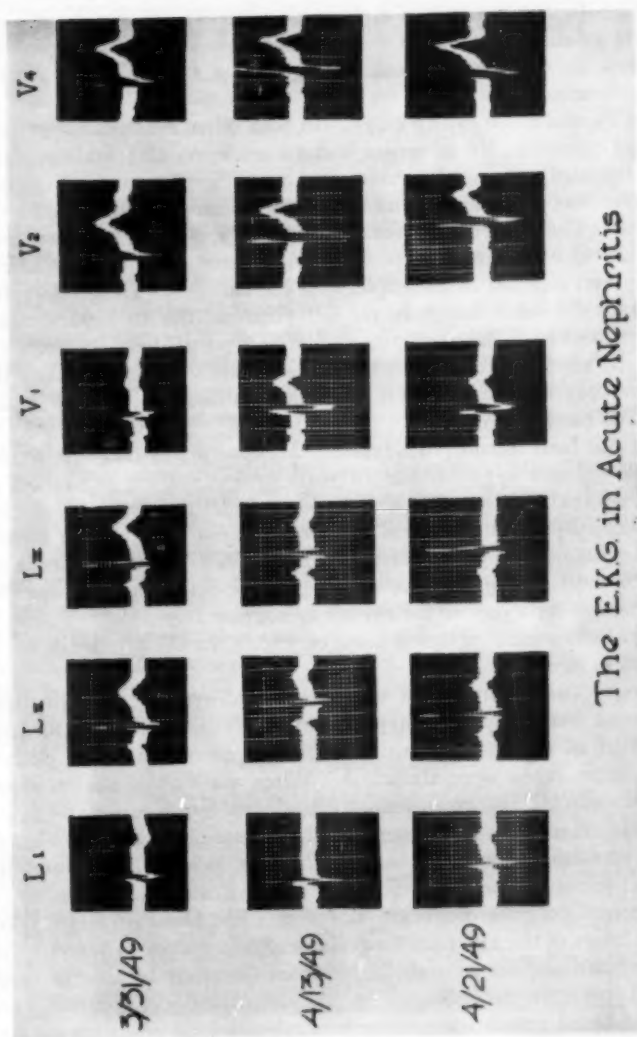
TABLE VIII
Type of Electrocardiographic Abnormality

	Occurring Alone	Combined	Total
Negative T ₁	2	8	10
Low T ₁	1	7	8
Negative T ₂	—	3	3
QT prolonged	1	6	7
Sinus tachycardia (100 or more)	0	3	3
Sinus bradycardia (60 or less)	0	6	6

Precordial leads were taken in all patients and consisted of CL₂ or CL₃ or CR₂ and CR₃ or CF₄. In four patients V leads were taken. Abnormalities in the precordial leads were noted in 15 of the 20 abnormal electrocardiograms. These consisted of T wave changes which in a few cases were low but in the majority of cases were inverted over the area of the left ventricle or in Leads CL₅, CR₄ or CF₄. All of these returned to normal except for two in which apparently the follow-up time was insufficient.

The characteristic T wave changes are most prominent in Lead I. First there is definite inversion of T₁; then, as there is a reversal to normal, T₁ becomes flat and, finally, upright.

The electrocardiographic changes did not keep pace with the clinical improvement. Whereas improvement was marked clinically at the end of



The E.K.G. in Acute Nephritis

FIG. 1. The T wave inversion present in Lead I has become low but upright, and it remained this way for another week. At the end of the third week the electrocardiogram returned to normal (4/13/49). QT is prolonged in Lead I, but this is found to be due to the U wave, which is depicted in the precordial leads. There is a slight change in the configuration in V₁. There is no great change in any of the other precordial leads.

a week in the typical case, the electrocardiographic changes returned to normal in 14 to 21 days. In seven out of 10 patients who showed inversion of T_1 the majority returned to normal within 30 days, varying between six and 90 days. In the remaining three with inversion of T_1 , insufficient tracings were taken to state when they became normal. In those patients who had a low T_1 , the T wave became upright more rapidly than when the T wave was inverted (five cases).

Diphasic T_2 was noted in two cases. In both other electrocardiographic findings were present. No comment can be made on this finding, since insufficient tracings were made. Also, an insufficient number of calcium determinations was done to determine the relationship of this ion to the Q-T changes. The various electrocardiographic abnormalities have been reported in 20 to 75 per cent of patients with acute nephritis.¹¹ Various factors have been stressed in the etiology of the changes. Langendorf and Pick²¹ postulated a local change in the left ventricle, due to sudden added stress of hypertension. Barnes²⁵ and Ash et al.²³ postulated essentially the same idea. It must be remembered that Goodhart's original paper² described a necropsy in which the left ventricle was dilated. This was also reported by Volhard.¹⁰

Age has also been considered a factor. Master⁷ states that the electrocardiographic changes in patients of 15 years or less are not so marked as in adults. Ash et al.,²³ in a report of 50 children under the age of 15, reports an incidence of 72 per cent. In our study age did not seem to be a significant factor. Six normal electrocardiograms of the 47 in this series were omitted from the following studies because of the failure to measure the blood pressure within a day of the electrocardiogram.

The typical electrocardiographic changes, except for the precordial leads, are illustrated in figure 1.

It was our clinical impression that electrocardiographic abnormalities are found most frequently with hypertension. Further evidence for this theory was that all severe hypertensives with convulsions in whom electrocardiograms were taken were abnormal. When we studied the incidence of electrocardiographic abnormalities associated with hypertension, we found little correlation if we took the highest blood pressure of the day the electrocardiogram was taken; but a definite correlation existed if we used the highest blood pressure before the electrocardiogram was taken.

In the normal electrocardiograms, 18 patients had blood pressures taken within eight hours of the electrocardiogram, and two within 24 hours. Six normal electrocardiograms were discarded from the study because of insufficient blood pressure recordings. In the abnormal electrocardiograms (20), 16 had blood pressure measurements taken within eight hours, four within 24 hours. In no instance was there an abnormal rise or fall of the blood pressure on the day of the electrocardiogram compared to the blood pressure on previous days. The results are as follows:

TABLE IX
Relation of Hypertension to Electrocardiographic Changes
(Blood Pressure Same Day)

Hypertension	Normal EKG	Per Cent	Abnormal EKG	Per Cent
Normal	7	35	9	45
Moderate	9	45	6	30
Severe	4	20	5	25
	<hr/>	<hr/>	<hr/>	<hr/>
Total	20	100	20	100

The above material was analyzed by Chi Square method, and from this study it was found that there is little relation between the height of the blood pressure on the day the electrocardiogram is taken and the abnormalities evidenced by the electrocardiogram (Chi Square = 1.27).

The desire of the physician for absolute rest and quiet for a patient with convulsions often led to the omission of supplementary procedures until the blood pressure had fallen and the danger of convulsions had diminished. For this reason the highest blood pressure prior to the taking of the electrocardiogram was used in the analysis of the electrocardiographic abnormalities.

In the abnormal electrocardiograms the highest blood pressure occurred within 10 days prior to the electrocardiogram in 16 cases, and in one other patient, hypertension existed 30 days prior to the electrocardiogram. In the remaining three patients with abnormal electrocardiograms and normal blood pressures, no hypertension at any time could be discovered in two. In the remaining case a convulsion had occurred 24 hours prior to admission, so that hypertension must have been present at that time, although the blood pressure was always within normal limits while the patient was in the hospital.

The following are the results:

TABLE X
Relation of Hypertension to Electrocardiographic Changes
(Highest Blood Pressure Prior to Electrocardiogram)

Hypertension	Normal EKG	Per Cent	Abnormal EKG	Per Cent
Normal	4	20	3	15
Moderate	10	50	5	25
Severe	6	30	12	60
	<hr/>	<hr/>	<hr/>	<hr/>
Total	20	100	20	100

The above material was analyzed by Chi Square method, and from this study it was found that there is a very high association between electrocardiographic abnormalities and previous hypertension. (Chi Square = 6.82 or significant on 2 per cent.) To state this in another way, in 98 cases

out of 100, electrocardiographic abnormalities will show a higher association with previous hypertension than with the blood pressure on the day of the electrocardiogram. This does not mean that all patients with abnormal electrocardiograms will have hypertension; rather, it means that electrocardiographic abnormalities are found in a significantly higher percentage of cases where hypertension is present if the blood pressure prior to the taking of the electrocardiogram is reviewed rather than any random determination on the day of the electrocardiogram. In all patients with convulsions the electrocardiograms were abnormal.

The relationship of cardiac enlargement to electrocardiographic abnormalities was variable. A normal electrocardiogram could be found with or without cardiac enlargement. (See case reports.) An abnormal electrocardiogram was most often associated with cardiac enlargement. If the heart was not enlarged the electrocardiogram was usually normal. An enlarged heart on x-ray was often found with a normal electrocardiogram.

Twenty patients had roentgenograms and electrocardiograms taken on the same day or within three days of each other. Eight of these showed a normal cardiac silhouette, and seven a normal electrocardiogram. In the eighth case the electrocardiogram was abnormal. A chest roentgenogram on the patient five months previously had shown essentially the same heart size as at the time of the abnormal electrocardiogram. Twelve of the patients whose roentgenograms showed cardiac enlargement had electrocardiograms taken within three days. Seven of the patients with enlarged hearts showed electrocardiographic changes and five showed none. These findings are summarized below:

TABLE XI
Relation of Cardiac Enlargement to Electrocardiographic Abnormalities

	Normal Heart	Enlarged
EKG normal	7	5
EKG abnormal	1	7

When clinical heart failure was present, x-ray examination showed that the heart was enlarged in all cases. Twenty-two patients had heart failure. Roentgenograms were taken in eight cases and cardiac enlargement was present in all. Electrocardiograms were taken in 12; they were abnormal in nine and normal in three.

DISCUSSION

Many causes have been considered in the pathogenesis of heart failure in acute nephritis. Chief among them is high blood pressure. In the 88 cases of acute nephritis studied, cardiac involvement was present in 41. Twenty-one of the 22 cases with heart failure in this series of 88 cases had moderate or severe hypertension. However, other factors have been considered. Cardozo²⁰ reported an increased blood volume in 16 of the 18

cases he studied. Addis²⁷ also emphasized the importance of hydremia as a probable factor in the cardiac failure of acute and subacute nephritis. Another factor is toxic changes associated with the nephritis itself, with acute myocardial changes or arteriolar capillary damage of the heart as well as of the entire body. The administration of large quantities of intravenous fluids may be a factor in producing heart failure in individuals whose heart is already under the strain of acute nephritis, especially when anuria or oliguria is present.

Hypertension in acute nephritis bears the same relationship to prognosis as the urinary findings do in diagnosis. If it is present, it should make one more cautious than ever, and if it persists, the outcome is nearly always bad. The immediate effect may be a sudden onset of heart failure with pulmonary edema and death. The major emphasis must be on the prevention of heart failure, or at least on the early treatment of it. When cardiac failure is obvious and advanced, treatment is often disappointing.

The low incidence of suspicion of heart failure in this series was an interesting finding and may have been due to several reasons. The edema of acute nephritis often may obscure distention of the cervical veins. Another reason may be hesitancy in making a diagnosis of heart failure in the absence of murmurs other than a systolic murmur at the apex. In the minds of many clinicians, cardiac failure is so intimately associated with adults that the diagnosis is often overlooked in children unless rheumatic fever is present. Gore and Saphir¹⁸ have also commented on this low incidence of the clinical suspicion of cardiac failure in acute nephritis.

Heart failure may be suspected if the pulse rate is accelerated, if there is beginning dilatation of the heart, if a systolic mitral murmur develops, if rales of pulmonary edema are heard at the bases of the lung, and if dyspnea or orthopnea is present, even in a mild form. The presence of a gallop rhythm is the most important clinical sign of imminent heart failure. Hypertension with heart failure was present in 21 of the 22 cases in this series. The remaining case illustrates that hypertension may occur and disappear before the heart failure becomes most severe. This patient had had a convulsion 24 hours prior to admission and had lain unattended during that time. It is fortunate that restriction of fluids, sedation and relief of the high blood pressure, the recognized treatment of convulsions, are also an ideal form of therapy for heart failure. It is probably this fact which is responsible for heart failure appearing in only nine of 16 patients with convulsions.

Cardiac enlargement, if on the basis of hypertension, would be expected to be greatest in those patients with convulsions, but this association was difficult to prove. The fear of precipitating further convulsions by taking an immediate x-ray causes most physicians to wait until the blood pressure has returned to normal. By the time this point is reached, cardiac enlargement may have disappeared.

The relative frequency of cardiac enlargement is not a major considera-

tion in acute nephritis, since the transitory increases in heart size and the great number of factors such as date of admission, time of x-ray, progression of nephritis with hypertension, and convulsions influence the incidence of cardiac enlargement. Rather, this study emphasizes the rapidity of the cardiac changes. Both LaDue²¹ and Master⁷ have illustrated this point.

LaDue and Ashman²² pointed out the high incidence of electrocardiographic changes in patients with cardiac enlargement. They investigated the problem by means of ventricular gradient studies. These authors believed that in 92.5 per cent of the patients with clockwise rotation of the gradient there was evidence of cardiac enlargement, while only 48 per cent with no deviation of the gradient showed an increase in the size of the heart. Our findings tend to corroborate this—that when the electrocardiogram is abnormal, usually the heart is enlarged, although the heart may be enlarged without an abnormal electrocardiogram. (See case report.)

The effect of hypertension on any of the manifestations of nephritis may be a subject for discussion. Especially is this true in the electrocardiographic findings. Ash et al.²³ found the incidence of cardiac involvement both clinically and by electrocardiogram to be greatest when the diastolic blood pressure was over 110 mm. of mercury. LaDue and Ashman,²² on analysis of their data by Chi Square, found the odds were six to one, that the blood pressure would be higher among those patients with rightward deviation of G than among those patients showing no abnormalities.

Master⁷ found little correlation between hypertension and the incidence of electrocardiographic abnormalities and heart failure. He pointed out that pheochromocytomas which result in severe hypertension do not produce these changes. We too found no relation between hypertension and electrocardiographic abnormalities if the blood pressure on the day the electrocardiogram was taken was used for analysis. However, it was noted that all patients who had convulsions had abnormal electrocardiograms. Since hypertension is so intimately related to convulsions, we believed it strange that there should be no relation between the two. The reason is that in patients with convulsions or threatened convulsions, all elective diagnostic procedures are postponed until the blood pressure is down and convulsions are no longer imminent. For this reason, the highest blood pressure prior to the taking of the electrocardiogram should be more of an index to the strain exerted by hypertension on the heart than that on the day of the electrocardiogram. This was shown to be true.

The diagnosis of cardiac failure may be difficult, especially in acute nephritis. Most important is the awareness of its high incidence in acute nephritis, and that it is one of the most common causes of death. Proper regulation of fluids, reduction of hypertension if possible, and cessation of all physical activity are imperative. In the 22 patients presented in this study, digitalization was employed in four instances, with insufficient dosage in one. Excellent results were seen in two cases. Cessation of dyspnea occurred in one and immediate diuresis in the other. In all except one of

the patients, digitalization was considered tardily. In acute nephritis, if dyspnea is present, treatment of heart failure must be instituted immediately.

However, the prevention of heart failure is more important than treatment after it has become established. It has been our experience that once acute pulmonary edema of left ventricular failure sets in, it is difficult to reverse the downward trend of the disorder. The edema observed in acute nephritis is seldom of serious significance, as it usually disappears when the acute inflammation of the kidney resolves. An interesting study on edema of acute nephritis by Peters²⁸ indicated that the chief disorder responsible for edema in acute glomerulonephritis is not the kidney disease but the congestive heart failure.

SUMMARY AND CONCLUSIONS

1. Eighty-eight cases of acute glomerulonephritis were studied with special reference to cardiac changes. If any one or combination of the following occurred, cardiac involvement was believed to be present: (a) the presence of clinical heart failure; (b) cardiac changes on x-ray examination; and (c) electrocardiographic abnormalities. Cardiac involvement was present in 41 cases (46.6 per cent).

2. A diagnosis of cardiac failure was established in 22 of the 88 cases. Cardiac failure was diagnosed more commonly in patients over 21 years of age, occurring in 10 of the 22 cases (45.5 per cent). The low incidence of heart failure in this series may have been due to several reasons: ignorance of the frequency of heart failure in acute nephritis; edema of acute nephritis possibly obscuring distention of the neck veins shrouding one of the chief evidences of heart failure; hesitancy to make a diagnosis of heart failure in the absence of murmurs other than a systolic murmur at the apex; and an overlooked diagnosis in children, unless rheumatic fever is present.

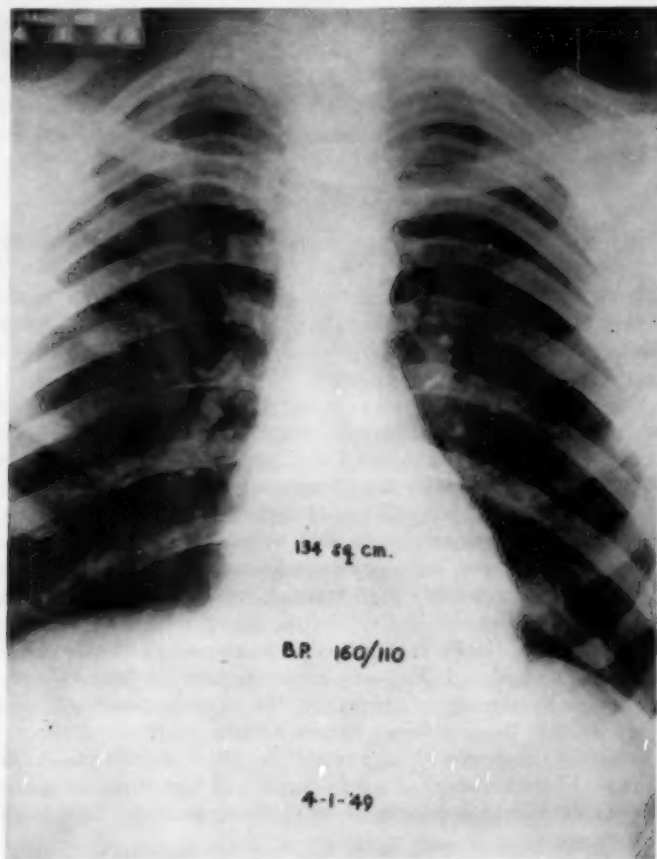
3. There was a close association between severe hypertension and cardiac failure. Cardiac failure was more frequent in patients with moderate or severe hypertension. However, the hypertension itself cannot be considered the sole cause of heart failure in most cases.

4. Teleroentgenograms were available in 29 of the 88 cases. Twelve were normal, 17 showed cardiac enlargement. In 8 patients, serial measurements of the cardiac area were made with demonstration of the changes in size of the heart.

5. Electrocardiograms were studied in 47 of the 88 cases. Twenty-six were normal, one was borderline and 20 were abnormal. The abnormalities most frequently noted were in the T wave changes in Lead I, which were either of low voltage or inverted. Electrocardiographic changes did not keep pace with clinical improvement, returning to normal in from 14 to 21 days.

6. While cardiac failure occurred in one fourth of the 88 cases, it occurred in nine of 16 patients who had convulsions. Electrocardiograms were all abnormal in patients with convulsions.

There was found to be little relation between the height of the blood pressure on the day an electrocardiogram was taken and the abnormalities evidenced by the electrocardiogram. However, a close relation exists between previous hypertension and electrocardiographic abnormalities.



A

FIG. 2 A, B, C. The complete measurements of case 7 are listed on page 515. The marked electrocardiographic abnormalities that can be seen with this slight amount of enlargement are demonstrated on page 517.

CASE REPORTS

The following case illustrates the minimal heart size changes that may occur with marked electrocardiographic alterations. The patient was not classified as having clinical heart failure.

Case 7. First Admission: A 10 year old white male entered the hospital on May 20, 1940, for acute rheumatic fever. He was discharged without sequelae on September 9, 1940.

He was examined many times for school athletics in the years that followed and no abnormalities were found. A preemployment urine examination in 1948 revealed a specific gravity of 1.018, negative sugar and albumin.

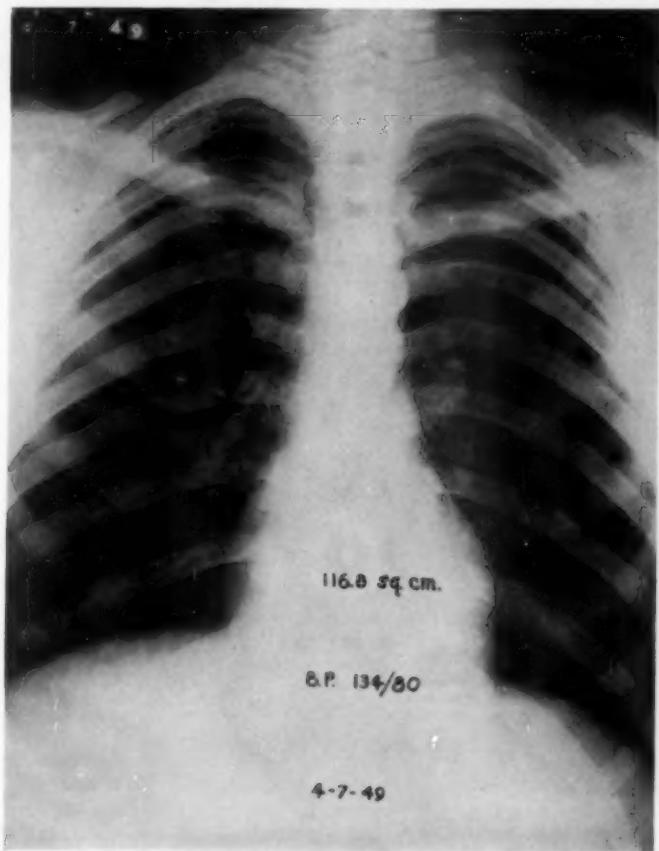


FIG. 2B

Second Admission: On March 30, 1949, at the age of 18, the patient reentered the hospital in a stuporous state with a history of a convulsive seizure two hours previously. Past history revealed that on March 13, 1949, the patient had noted a toothache and had sought dental attention. A hole was drilled in the tooth and extraction was scheduled for March 19. The patient failed to keep the appointment. On March 22 he sought medical advice for backache and dark colored urine. The private physician stated that the urine had 40 to 50 red blood cells per high power

field. Except for swelling of the face on the side of the infected tooth, examination was essentially negative. Blood pressure was 130/80 mm. of Hg. Following preparatory penicillin, the tooth was extracted on March 26. The patient was asymptomatic on March 27 and 28, although the blood pressure had risen to 150/96 mm. of Hg on March 28, and cellular elements were still present in the urine. He continued to be ambulatory and asymptomatic on March 29 except for a slight headache. On March 30 he noted an increase in the severity of the headache and blurring of vision;

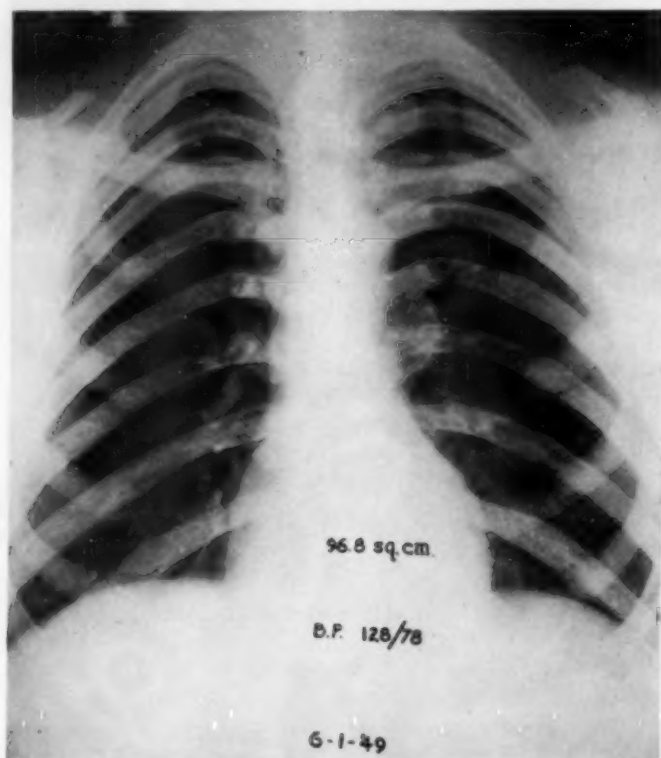


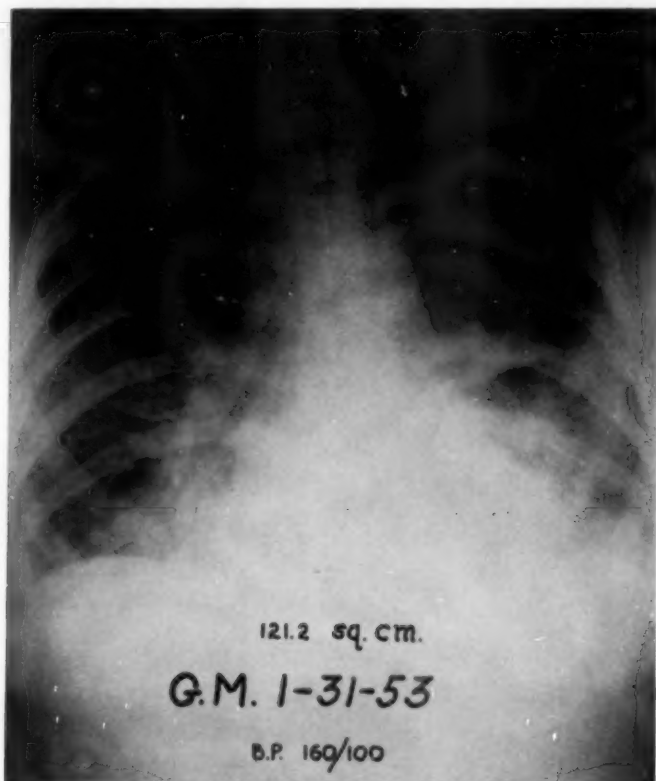
FIG. 2C

on the way to the doctor's office he had a generalized convulsion and was admitted to the hospital.

Physical Examination: This revealed a thin white male complaining of headache. The temperature was 100° F., the pulse 72, and the blood pressure 190/120 mm. of Hg. Positive physical findings revealed a drowsy, cooperative white male, with periorbital edema. Pupils reacted to light and accommodation. Ophthalmoscopic examination showed retinal edema but was essentially negative except for post-traumatic scarring of the retina of the left eye. There was a healing tooth socket of the second right molar. The neck showed no venous distention. The heart was enlarged, with an apical impulse 1 cm. outside the midclavicular line. There was a grade 2 apical sys-

toxic murmur and a grade 1 pulmonic systolic murmur. P_2 was louder than A_2 . A sinus rhythm was present. The liver, kidney and spleen were not palpable. There was tenderness over both costovertebral areas. There was no edema of the extremities. The remainder of the examination was essentially negative.

Laboratory Examination: The urine showed a specific gravity of 1.015; albumin, 4 plus; red blood cells over 200 per high power field, 5 to 8 white blood cells, and



A

Fig. 3 A, B, C, D. The complete measurements of case 8 are listed on page 515. There were no electrocardiographic abnormalities.

occasional hyaline casts. Blood cultures were negative. On admission the red blood count was 4,360,000; white blood count, 12,000, with 18 per cent nonsegmented and 73 per cent segmented neutrophils, 3 per cent monocytes and 6 per cent lymphocytes. Kline reaction was negative. Sedimentation rate was 74/101 mm. in one hour. Anti-streptolysin titer was 500 units. Total protein was 7.60 gm. per cent (albumin, 4.13 gm. per cent; globulin, 3.47 gm. per cent). Blood chemistry values were as follows: serum sodium, 136 mEq./L.; serum potassium, 4.14 mEq./L.; carbon dioxide com-

binning power, 50.2 vol. per cent; serum calcium, 9.2 mg. per cent; nonprotein nitrogen, 35.3 mg. per cent. An intravenous pyelogram was negative.

Course in Hospital: Approximately one hour after his admission another convulsion occurred. Auscultation of the heart immediately after this convulsion had ceased revealed the same murmurs as were present on admission, but in addition a definite diastolic gallop rhythm was present. The gallop persisted for one hour. Following this initial stormy course, the remainder of the clinical course was comparatively routine. The weight on admission was 164½ pounds, fell to 152 pounds

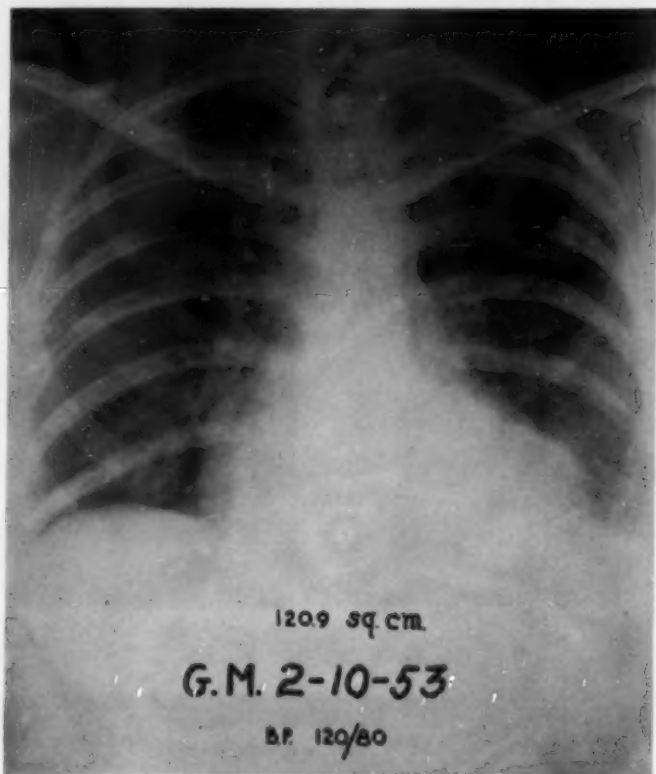


FIG. 3B

in six days, and remained at this level for the remaining 60 hospital days. The electrocardiogram returned to normal in 21 days. The cardiac enlargement, which was minimal on admission and would most probably have been called normal if only one film had been taken, progressively diminished in size and became stationary in 21 days and stayed at approximately this figure for the next four years. At the present time this patient's nephritis is chronic.

The accompanying x-rays demonstrate the minimal enlargement that was present and the gradual regression (figure 2).

Case 8 illustrates the definite changes in size of the heart that may occur with no electrocardiographic changes.

Case 8. A 30 year old white married female was first seen on January 29, 1953, with a history of a sore throat three weeks prior to admission. This cleared on specific therapy and the patient felt well until two weeks before admission, when dark urine was noted, followed by an insidious weight gain of 20 pounds. One week

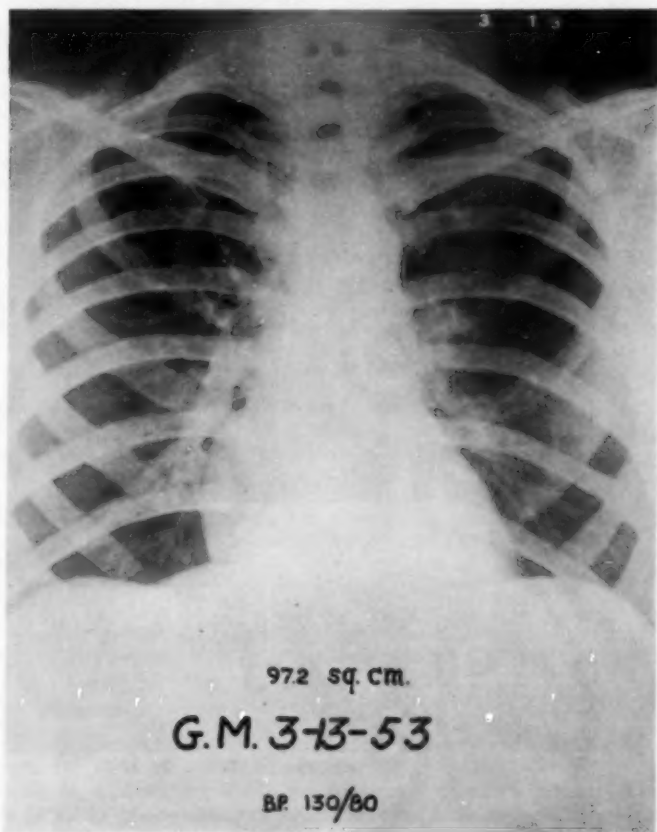


FIG. 3C

prior to her admission headache, ankle edema and dyspnea on exertion occurred, which slowly became progressive. Nocturnal dyspnea, cough and orthopnea had been present the first 48 hours.

Physical Examination: This revealed a dyspneic white female sitting up in bed. Her weight was 177½ pounds. Temperature was 103° F. and blood pressure was 160/100 mm. of Hg. The eyes showed slight periorbital edema. Ophthalmoscopic examination was negative except for increased retinal highlights. The throat was

mildly reddened. Distention of cervical veins was carefully looked for but was not found; there was mild edema of the neck. The heart was enlarged to the left, and sinus rhythm was found at a rate of 120. There were apical and basilar systolic murmurs. A_2 was louder than P_2 . P_2 was reduplicated. There was slight dullness in both bases, with expiratory wheezes throughout the lung fields. The liver edge was felt two fingerbreadths beneath the costal margin. Extremities revealed 1 plus pitting edema.



FIG. 3D

Laboratory Examination: The urine showed a specific gravity of 1.025; albumin, 4 plus; red blood cells and white blood cells were numerous. Granular, red blood cell and white blood cell casts were seen. The red blood count was 4,050,000; white blood cells, 5,000, with 2 per cent nonsegmented and 52 per cent segmented neutrophils, 38 per cent lymphocytes, 2 per cent monocytes and 6 per cent eosinophils. Color index was .96. Total protein was 8.1 gm. per cent (albumin, 4.75 gm. per cent; globulin, 3.36 gm. per cent). Nonprotein nitrogen was 30 mg. per cent. Sedimentation rate was 60 mm. in one hour. Hemoglobin was 12 gm., or 77.5 per cent. Roentgenograms showed definite cardiac enlargement and pulmonary congestion (figure 3). The intravenous pyelogram was normal. The electrocardiogram was normal.

Course in Hospital: The patient was sedated with magnesium sulfate and immediately digitalized with 8 c.c. of intravenous Cedilanid. Dyspnea improved in about two hours and disappeared, together with the orthopnea, in 24 hours. The patient was placed on oxygen at 6 L. per minute by nasal catheter. Other medications in appropriate dosage included Hycodan, penicillin and Apresoline. On the following day the headache was much improved and dyspnea had disappeared. The heart was smaller to physical examination; the rate was 88; P_2 was no longer reduplicated. Blood pressure was 150/90 mm. of Hg. The urinary output continued at about 500 c.c. per 24 hours. On the second hospital day the blood pressure fell to 140/80 mm. of Hg, the heart was regular at 86. The lungs continued to have scattered râles and expiratory wheezes. On the third hospital day the urinary output rose to 1,100 c.c., and on the fourth hospital day to 1,900 c.c. The patient's progress thereafter was comparatively smooth. She lost 23 pounds in 13 days. She was discharged on the thirteenth hospital day, at which time her weight was 154 pounds. Blood pressure was 120/80 mm. of Hg, and physical examination was essentially negative. She continued on Digoxin, .25 mg. a day for one month, and has remained asymptomatic. There has not been complete clearing of the urine six months after her hospital admission.

ACKNOWLEDGMENT

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SERUM CHOLINESTERASE ACTIVITY IN THE NORMAL INDIVIDUAL AND IN PEOPLE WITH LIVER DISEASE *

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THE purpose of this study was to evaluate the serum cholinesterase activity as a test of liver function. Previous investigators, using various technical procedures, reported a wide range of normal values. They indicated, however, that the test had considerable merit, since it appeared to be a direct test of liver function which did not depend on any abnormality of the protein fractions.

SERUM COLINESTERASE IN HEALTH AND DISEASE

Brauer and Root¹ and Ellis, Sanders, Shirley and Bodansky² showed that when rat livers were damaged by carbon tetrachloride the serum cholinesterase was lowered. This finding would suggest that the enzyme was produced in the liver. Steensholt and Venndt³ administered carbon tetrachloride to dogs and found that the albumin dropped and the serum cholinesterase went up. Brauer and Root⁴ also found that administration of carbon tetrachloride to dogs resulted in a rise in plasma cholinesterase, but after one to four days it dropped below normal. The latter can be explained by the fact that there is considerable cholinesterase in the liver, and when damage occurs there is an outpouring of this enzyme. This results in an increase of plasma level. After this it drops, owing to deficient formation of the enzyme. Hall and Lucas⁵ and Milhorat⁶ found that there was no correlation between serum cholinesterase activity and age, sex, diet, heart rate, blood pressure, body weight or muscle mass. Sawitsky, Fitch and Meyer⁷ reported that cholinesterase activity is fairly constant for each individual but varies widely from one individual to another. Mahal⁸ found that sleeplessness, change in surrounding temperature, fasting or glucose feeding has no effect on the cholinesterase content of the blood. Subcutaneous injections of strychnine sulfate, morphine or cobra venom have no effect on the cholinesterase content of the blood. Croft and Richter⁹ observed that serum cholinesterase rises during muscular exercise. Adrenalin, ergotamine and histamine have no effect. There is a rise in serum cholinesterase during circulatory stasis, due to an increase in concentration of serum proteins. Stoner and Wilson¹⁰ could not corroborate the fact that cholinesterase activity changed as a result of muscular activity.

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Brauer¹¹ and others^{12, 13, 14, 15, 16, 17, 18, 19, 20} observed that serum cholinesterase activity was low in liver disease and normal in obstructive jaundice. Brauer¹¹ reported low readings in anemia and cachectic states. Cases of constipation had elevated values. Levine and Hoyt²¹ had low readings in neoplasm and pregnancy, and normal readings in tuberculosis. Butt, Comfort, Dry and Osterberg¹³ found normal values in hypertension, heart disease and pancreatic disease. Schifrin, Tuchman and Antopol¹⁴ observed that any disease producing cachexia produces a low cholinesterase of the serum. McArdle¹⁶ reported normal cholinesterase activity of serum in diabetes and hyperthyroidism. Antopol, Tuchman and Schifrin²² obtained relatively elevated serum cholinesterase in hyperthyroidism. Molander, Friedman and LaDue¹⁵ obtained low serum cholinesterase levels in malignancy with metastases and lymphomas. They could follow the improvement of lymphomas with rise in cholinesterase of serum back to normal after therapy. Dikshit and Mahal²³ produced toxemia in guinea pigs which lowered the cholinesterase values of the serum. In the animal which survived, the activity of the enzyme slowly returned to normal. Jones and Stadie²⁴ found low serum cholinesterase activity in far advanced tuberculosis and carcinoma.

Sawyer and Everett²⁵ reasoned that the liver was the chief area of formation of nonspecific cholinesterase, since only liver and gonads display marked activity of this enzyme. Gonads are not necessary for synthesis, since castrates respond to administration of estrogen by elevation of the serum cholinesterase. Liver also has a higher content of nonspecific cholinesterase than serum. Liver produces serum albumin, and depression of serum cholinesterase has been associated with depressed serum albumin. In the *Transactions of the Fifth Conference on Liver Injury* in 1946,²⁶ it was brought out that strong evidence exists that the serum enzyme is elaborated by the liver. Levels of serum cholinesterase fall toward zero in animals with total hepatectomy or those poisoned with carbon tetrachloride. Serum activity is very stable from day to day in one individual and is not changed by exercise, environment or food. It has never achieved wide prominence as a liver function test because of wide variation of normal figures. It is now an established fact that serum cholinesterase is low in liver dysfunction. Wescoe, Hunt, Riker and Litt²⁷ observed that serum cholinesterase activity in patients with liver disease is depressed below normal levels. Subsequent to administration of diisopropyl fluorophosphate, the regeneration rate of serum cholinesterase in patients with liver damage is significantly slower than in normal subjects. These data offer further proof that the liver is the primary site of formation of serum cholinesterase.

Faber^{28, 29} noted that low serum albumin was associated with low cholinesterase. The most plausible explanation is that albumin and cholinesterase are both secreted into the serum from the same cells and in a fairly constant ratio. Since serum albumin is produced in liver, serum cholinesterase must also be produced in that organ. Also, cholinesterase rises in albuminuria.

This accumulation of cholinesterase is presumably due to a smaller urine loss compared with a large loss of albumin. The ratio, however, remains constant, probably because of commonplace origin. Levine and Hoyt³⁰ noted that states with low albumin were associated with low cholinesterase values and vice versa, with one exception—if albumin is low due to urinary excretion, the cholinesterase in many cases is normal or higher than normal.

Davis³¹ noted that incubated liver extract or pteroylglutamic acid with certain dog sera caused increase in cholinesterase activity. Injection of these substances into dogs depleted of cholinesterase by diisopropyl fluorophosphate injection caused more rapid regeneration of the enzyme activity than in the untreated ones. Sawitsky³² noted cholinesterase activity greater than normal in patients with pernicious anemia in early remission, sickle cell anemia, and hypochromic macrocytic anemia. Cholinesterase is depressed in pernicious anemia in relapse, in leukemia and in myelophthisic anemias. Normal cholinesterase levels are found in Hodgkin's disease, leukemia and polycythemia vera. Kunkel, Krop and Wescoe³³ observed that liver extract and folic acid *in vivo* and *in vitro* do not increase plasma cholinesterase activity in normal or in plasma-cholinesterase-depleted dogs. Sabine³⁵ in 1940 noted that in untreated severe pernicious anemia there was a marked reduction in plasma and red blood cell cholinesterase. With treatment, there was an immediate sharp rise. High levels were maintained and gradually leveled off.

DETERMINATION OF CHOLINESTERASE OF THE SERUM

Twenty cubic centimeters of 0.01 molar solution of acetylcholine are placed in a beaker, and this is corrected to pH 8 with .01 normal sodium hydroxide. Then 0.2 ml. of serum or plasma is added to the solution and it is incubated in a water bath for 30 minutes. The pH is measured by a Beckmann pH meter and is kept at level 8 throughout the entire experiment by titrating every five minutes with normal .01 sodium hydroxide. The temperature of the water bath is kept at 30° C. The values are expressed as the number of cubic centimeters of sodium hydroxide utilized in the neutralization of the acetic acid formed.

DETERMINATION OF CHOLINESTERASE OF THE RED BLOOD CELL

For this procedure 5 c.c. of blood are drawn into a test tube containing heparin, and this is mixed thoroughly to prevent the blood from clotting. The blood is then centrifuged at 20,000 revolutions per minute for 15 minutes in a graduated centrifuge tube and the plasma separated. The cells are then mixed with two or three volumes of physiologic saline and again centrifuged at 20,000 revolutions per minute for 15 minutes. After the supernatant fluid is discarded this operation is repeated, this time for 20 minutes. The volume of the cells is noted, and then the saline supernatant is removed to the point where the remaining volume of cells and saline is

twice the volume of the cells alone. The cells are then mixed thoroughly with the remaining saline. After mixing, 0.4 mm. of cell suspension is hemolyzed in 9.6 mm. of 0.01 per cent saponin solution. One millimeter of hemolyzed red cell solution, which represents 0.2 mm. of cells, is added

TABLE I
Serum and Red Blood Cell Cholinesterase in Normal Individuals

Males		Females	
Serum	RBC	Serum	RBC
2.29	0.88	2.14	0.83
2.67	1.17	1.92	0.50
3.09	0.89	2.55	0.44
2.65	0.72	1.61	0.38
2.52	0.58	1.72	0.75
1.75	0.62	1.71	0.87
2.12	0.66	1.65	0.70
1.54	0.71	1.57	0.94
1.94	0.69	1.86	0.27
1.82	0.78	1.15	0.47
1.95	0.57	1.69	0.94
1.75	0.67	2.59	0.83
1.92	0.83	1.35	0.86
1.92	0.81	1.84	0.55
1.46	0.86	1.65	0.76
1.15	0.75	1.68	0.93
1.70	0.79	1.22	0.81
1.86	0.93	1.27	0.79
1.04	0.67	1.25	0.93
1.06	0.60	1.59	0.82
1.52	0.59	1.70	0.69
1.67	1.02	1.92	0.73
1.40	0.57	1.48	0.93
2.13	0.93	1.35	0.85
1.23	0.70	1.21	0.56
1.83	0.56	1.37	0.66
1.91	0.85	1.30	0.57
1.78	0.69	1.24	0.49
2.10	1.03	1.04	0.75
1.92	1.05	1.03	0.69
1.93	1.07	1.13	0.75
1.65	0.75	1.15	0.60
2.23	0.80	1.04	0.63
1.32	0.52	1.18	0.71
1.75	0.94	1.08	0.81
1.16		1.39	0.55
1.24	0.56	1.44	0.82
1.32	0.58	1.26	0.71
1.03	0.91	1.43	0.57
1.51	0.93	1.40	0.66
1.59	0.92	1.52	1.04
1.09	1.05	1.70	0.85
2.02	0.86	2.27	1.12
1.16	1.16	2.14	0.79
2.26	1.16	1.44	1.00
2.60	1.20	1.89	0.95
2.76	1.11	1.55	0.70
3.27	0.91	2.17	0.63
2.54	1.34	1.88	1.22
		1.42	0.62
		2.15	1.25

to the solution of 20 c.c. of acetylcholine and then titrated with 0.01 N sodium hydroxide. The value is again expressed as the number of cubic centimeters of 0.01 N sodium hydroxide required to neutralize the acetic acid produced by the interaction of cholinesterase in acetylcholine.

SERUM AND BLOOD CHOLINESTERASE VALUES IN NORMAL PEOPLE AND IN PATIENTS WITH LIVER DISEASE

Serum cholinesterase as a test of liver function has been known for about 15 years. Its use has not been very widely accepted, owing to variability of the normal values. However, it was thought by this observer, after review of the literature, that this may be a valuable test of liver function and that perhaps the wide range of serum values in normal patients resulted from indiscriminate selection of material. In the present investigation, 100 normal healthy individuals were selected from the employees of the Wood Veterans' Hospital. The first 20 subjects were studied both before and after meals.

Activity of red blood cell cholinesterase was studied with and without the addition of potassium chloride in various dilutions, since its action is potentiated by this electrolyte. It was found that 0.5 c.c. of a one molar solution was adequate to potentiate the action of true cholinesterase.

CHOLINESTERASE IN NORMAL INDIVIDUALS

The 100 normal individuals studied included 49 males and 51 females. The serum or pseudocholinesterase values expressed as the number of cubic centimeters of 0.01 N sodium hydroxide necessary to neutralize acetic acid formed varied between 1.00 and 3.27. The serum cholinesterase values in males varied from 1.03 to 3.27. The mean was 1.848, with a standard deviation of the mean of 0.535 (table 1). The female values varied between 1.03 and 2.59, with a mean of 1.569 and a standard deviation of the mean of 0.383 (table 1). The red blood cell cholinesterase varied between 0.27 and 1.34 c.c. of sodium hydroxide. The male values varied between 0.52 and 1.34, with a mean of 0.844 and a standard deviation of 0.2103 (table 1); while the female values varied between 0.27 and 1.25, with a mean of 0.752 and a standard deviation of the mean of 0.1945 (table 1).

CHOLINESTERASE BEFORE AND AFTER MEALS

Serum and red blood cell cholinesterase determinations were done before and one and one-half hours after breakfast. The serum cholinesterase did not change after meals in 20 people studied, while the red blood cell cholinesterase fell after meals in 46 people studied (table 2). This was a consistent finding and was not the same in every patient. It was thought that perhaps the drop was due to an increase of hydrochloric acid in the gastric juice, or perhaps to altered permeability of cells during digestion. Greig³⁶ has pointed out that cells poisoned with cholinesterase are more permeable.

Further investigation was made to determine the cause for the change. Therefore, red blood cell cholinesterase determinations were done on 12 patients having gastric analysis before and after stimulation of the gastric mucosa with 7.5 per cent alcohol, five of whom showed a drop in cholinesterase. The drop took place in all patients who had an increase of HCl after stimulation. However, other patients who had an increase in gastric acidity did not show a drop (table 3). Red blood cell cholinesterase was

TABLE II
Serum and Red Blood Cell Cholinesterase before and after Meals
in Normal Individuals

Ser. CE. Before Meals	Ser. CE. After Meals	RBC CE. Before Meals	RBC CE. After Meals
2.14	2.10	0.83	0.68
2.29	2.33	0.88	0.67
2.67	2.71	1.17	0.97
1.92	1.94	0.50	0.33
3.09	3.10	0.89	0.69
2.65	2.68	0.72	0.30
2.55	2.55	0.44	0.29
1.61	1.62	0.38	0.25
2.52	2.59	0.58	0.38
1.72	1.70	0.45	0.32
1.71	1.71	0.87	0.51
1.75	1.83	0.62	0.40
2.12	2.10	0.66	0.52
1.54	1.53	0.71	0.43
1.94	1.93	0.69	0.53
1.82	1.90	0.78	0.61
1.65	1.67	0.70	0.44
1.57	1.55	0.94	0.78
1.95	1.90	0.57	0.32
1.75	1.75	0.76	0.55
		0.66	0.48
		0.92	0.72
		1.19	0.89
		1.54	1.16
		1.16	0.91
		0.85	0.67
		1.24	0.98
		0.98	0.66
		1.05	0.91
		0.79	0.54
		0.87	0.75
		0.66	0.57
		1.08	0.89
		0.82	0.63
		0.77	0.65
		0.93	0.78
		0.70	0.54
		0.67	0.40
		0.75	0.51
		0.65	0.50
		0.73	0.61
		0.78	0.53
		0.60	0.48
		0.87	0.73
		0.78	0.65
		0.85	0.77
		0.74	0.63

TABLE III
Red Blood Cell Cholinesterase before and after Gastric Stimulation
with 7½ Per Cent Alcohol

Before Stim. with 7½ Alc.	After Stim. with 7½ Alc.	Units Change in Gastric Acidity
0.72	0.66	59-70
0.59	0.62	0-38
0.51	0.69	60-72
0.66	0.50	0-20
0.66	0.46	0- 6
0.79	0.89	20-70
0.75	0.62	48-42
0.94	0.75	0-28
0.62	0.80	55-34
0.66	0.72	18- 0
0.68	0.58	0-40
0.85	0.64	0-20

then determined before and after a gastrointestinal series, and a consistent drop in all cases was shown (table 4). With this latter finding (particularly since none of the barium was absorbed) it was thought that perhaps the drop of red blood cell or true cholinesterase after meals was due to increased gastrointestinal motility, causing a withdrawal of cholinesterase from the red cell and concentrating it at the myoneural junction. It was concluded that this probably was not due to an increase of free hydrochloric acid in the stomach but might be due to motility. Serum cholinesterase de-

TABLE IV
Red Blood Cell Cholinesterase before and after Gastrointestinal Series

Before	After
1.08	0.75
0.68	0.57
0.58	0.40
0.91	0.52
0.84	0.73
1.58	0.91
1.03	0.89
1.04	0.90

termination of one normal healthy male was carried out every three hours throughout the day and was found not to vary.

SERUM CHOLINESTERASE IN LIVER DISEASE AND VARIOUS PATHOLOGIC STATES

Serum cholinesterase determinations were made in various diseases. In cirrhosis, of 28 cases studied, 25 had low values and three had borderline results. Table 5 shows this liver function test in comparison with others. Five cases of hepatitis studied all had low values (table 5). One was followed to recovery and, as he improved, the serum cholinesterase rose. Of 12 patients with Hodgkin's disease, four showed normal values and eight low values, three of whom had definite liver damage (table 6). Of three cases of chronic leukemia studied, one had a low value, one was borderline and one was normal. Two cases of multiple myeloma had low values.

TABLE V
Serum Cholinesterase in Cirrhosis Compared with Other Liver Tests

Ser. CE.	BSP	Thymol Turbidity	Pro. Time	Zn Sulf. Turbidity	Total Ser. Bilirubin
0.78	31%	5.5	33%	18.7	5.8
0.40	32%	12.2	57%	30.0	1.9
0.28	41%	4.6	46%	27.0	2.8
0.69	8%	7.4	100%	15.0	0.6
0.58	14%	10.9	32.6%		2.6
0.83	21%	3.4	100%	27.4	0.8
0.88	38%	6.4	63.5%		1.2
0.41	37%	11.5	52%	33.6	2.2
0.59	8%	4.5	89%	20.8	0.8
0.63	34%	9.6	66.2%	19.4	2.9
0.51	26%	10.2	46%	33.6	2.4
0.27	17%	13.0	55%	27.4	1.9
0.99	21%	7.4	66.2%	28.2	2.6
0.83		5.0	83%	12.6	2.4
0.54	5%	16.2	55%	33.6	0.8
0.74					
1.06					
0.62					
1.17					
0.53					
0.66					
0.64					
1.06					
0.57					
0.48					
0.30					
0.82					
0.71					

Serum Cholinesterase in Hepatitis Compared with Other Liver Tests

Ser. CE.	BSP	Thymol Turbidity	Pro. Time	Zn Sulf. Turbidity	Total Ser. Bilirubin
0.55	9%	10.2	70%	18.0	6.6
0.84	30%	5.9	65%	20.1	0.8
0.97	36%	37.4	77%	26.6	7.7
0.63	3%	16.2	52%	23.5	2.9
1.01-1.42					
0.85					

Nine terminal cases of carcinoma had low values. One case each of lupus erythematosus, polycythemia rubra vera, and glomerulonephritis with a low serum albumin had normal values. One case of idiopathic hyperlipemia had a borderline result (table 6).

SERUM CHOLINESTERASE BEFORE AND AFTER SURGERY

It is known that, with general anesthesia, patients postoperatively usually have some liver damage. Patients were studied preoperatively and postoperatively to determine whether enough liver damage took place to alter the test, or whether stress altered the serum cholinesterase reaction. Patients with general and spinal anesthesia as well as local anesthesia were studied. One patient had a tonsillectomy and showed a drop of 0.17 c.c.

TABLE VI
Serum Cholinesterase Compared with Other Liver Function
Tests in Various Pathologic States

Disease	C.E.	HSP	Thymol Turbidity	Proth. Time	Zn Sulf. Turbidity	Total Ser. Bilirubin	T.P. & A/G Ratio
Cancer of Pancreas	0.35		9.0	22.2%	8.4	23.4	4.95-2.92/2.03
Idiopathic Hyperlipemia	1.06	0%	18.0	66.2%	41.6	1.0	7.26-3.45/3.81
Cancer of Stomach with Metastases	0.34	31%	3.8	66.2%	14.4	16.1	5.15-2.55/2.60
Lymphoma with Liver Involvement	0.45	27%	2.2	81%	6.4	9.9	6.24-4.47/1.77
Lymphoma	0.50	3%	2.6	43.5%		0.6	
Lymphoma	0.81	2%	5.0	77%	15.0	1.0	
Acute Lymphatic Leukemia	0.67	7%	2.6	72%		1.7	6.58-4.26/1.82
Lymphoma	0.24	5%	5.5	55%		0.4	5.87-3.45/2.42
Lymphoma with Liver Involvement	0.27	14%	2.2	55%	6.9	1.0	5.50-3.81/1.69
Metastatic Melanosarcoma	0.38	3%	6.9	67%			5.37-3.15/2.22
Lymphoma	0.79	17%	2.2	75%		0.8	7.15-5.06/2.09
Mult. Myeloma	0.52	3%	2.2	55%	102.4	0.4	15.71-2.55/13.16
Lymphoma	1.25	2%				0.6	7.60-5.13/2.47
Lymphoma	1.21	10%	2.6	68%		0.4	7.72-4.70/2.52
Lymphoma with Liver Involvement	0.30	29%	8.4	55%	34.8	9.6	6.23-2.82/3.21
Mult. Myeloma	0.82	4%	8.4	55%	68.8	0.6	13.21-2.52/10.69
Chronic Lymphatic Leukemia	1.08	2%	7.4	63.5%		0.8	6.47-4.37/2.10
Lymphoma	0.93	6%	7.9	72%			7.67-3.87/3.80
Lymphoma	1.56	0%	8.4	75%			7.03-5.13/1.90
Myeloid Metaplasia	0.57	7%	4.2	43.5%	10.2	0.4	5.08-3.68/1.40
Pernicious Anemia	0.88		6.4	63.5%	13.0	3.4	6.93-4.99/1.94
Pernicious Anemia	1.32	8%	5.9	73%		0.8	
Lupus Erythematosus	1.11	4%	5.0	100%			
Aplastic Anemia	0.89	2%	3.8	80%			6.77-5.13/1.64
Polycythemia Vera	1.11	6%	1.2	66.2%		1.9	7.00-5.00/2.00
Nephrotic Syndrome	1.94						4.28-2.40/1.88
Chronic Lymphatic Leukemia	1.15	3%	2.2	74%		0.4	4.74-3.13/1.61
Hypernephroma	0.27	2%	9.0	80%		0.8	6.51-3.75/2.76
Cancer of the Pancreas	0.27	100%	6.4	46%	9.0	28.8	6.28-3.01/3.27

TABLE VII
Serum Cholinesterase before and after Surgery

Type of Anesthesia	Type of Surgery	Before Surgery	After 1½ Hrs.	4 Hrs.	21 Hrs.	29 Hrs.	48 Hrs.	70 Hrs.	93 Hrs.
Local	T&A	1.97	1.80						
Spinal	Prostatic resection	1.61	1.43						
Spinal	Vein ligation	1.37	1.20						
Spinal	Hernia repair	1.75	1.54						
Spinal	Osteotomy	2.14	1.90						
General	Laminectomy	1.40	1.80	1.69	1.48	1.23	1.19		1.24
General	Duodenal diverticulum	1.46	1.58	1.86	1.70	1.39	1.20		1.26
General	Gastric resection	1.27	1.85		1.73		1.42		
General	Exp. right ankle	2.14		2.32		1.82		2.22	
General	Nephrolithiasis	1.81	1.91		1.60			1.83	
General	Thyroid adenoma	1.75		2.16		1.92		1.85	

one and one-half hours after operation. This was considered significant. Four cases were done before and after spinal anesthesia and all four showed a drop one and one-half hours postoperatively (table 7). Six cases were done before and after general anesthesia. All had a rise in serum cholinesterase at one and one-half hours, and all but two dropped at the 24 to 68 hour determinations.

SERUM CHOLINESTERASE BEFORE AND AFTER ACTH ADMINISTRATION

To determine if any of the decreases in cholinesterase were related to stress when the patients were under spinal anesthesia, two patients were studied before and after ACTH injections (table 8). The Thorn test was

TABLE VIII
Serum Cholinesterase before and after ACTH

Before	2 Hrs. After	4 Hrs. After
1.65	1.21	1.29
1.05	1.01	0.89

performed, using 25 mg. of ACTH. One patient showed a drop in serum cholinesterase after two hours and remained low after four hours of injection of ACTH. One patient showed no drop at the two hour period but had a drop at the four hour period.

DISCUSSION

The use of the serum cholinesterase level as a test of liver function is not new. The test has not achieved widespread popularity, however, owing to the wide range of normal results obtained. The test is easy to perform and quite accurate, and I believe the margin of error is very small. It is very difficult to compare our results with those of other investigators using a titration method, because of many differences in technic. Taking these differences into account, our results do not vary greatly from those of others.

It has been reported by numerous investigators^{12, 14, 16, 18, 20} that in obstructive jaundice the values are normal. In liver disease, results below normal have been obtained.^{12, 18, 20, 14, 16, 18, 20} We did not do tests on any patients with benign obstruction, but in those with malignancy with obstructive jaundice the results showed impaired liver function or low serum albumin. A low serum albumin was present in two of our patients who were terminal. This is brought out in table 6. The patients who had a reduced serum albumin also had serum cholinesterase levels which were diminished. All but three of our cases of cirrhosis and all of our cases of hepatitis had low serum cholinesterase levels. One case of hepatitis was followed to recovery, and as the patient improved the serum cholinesterase returned to normal.

The fact that nonspecific cholinesterase is produced in the liver cells would appear to give this test an advantage over the flocculation and turbidity tests. These latter types of procedures are by no means an index

of liver function but indicate only abnormalities in serum proteins. Vorhaus et al.²⁷ found that serum cholinesterase was low in liver disease and that it rose with clinical improvement, as was demonstrated in one case of hepatitis in this investigation. They thought this test a more sensitive index of improvement than any other liver function test. It can be seen from table 5 that the test is reliable in comparison. It can be concluded that this is a valuable and reliable test, not only for liver function but also for the differential diagnosis of jaundice and for following the changes in liver function.

It was thought desirable, in tests on normal people, to make cholinesterase determinations before and after meals on serum and red blood cells. It was found that the red blood cell cholinesterase level falls after meals. This had not been reported previously. It was a consistent finding and was thought to be significant. A standard error of the difference between the two means was determined, and it was found that the difference before and after meals was mathematically significant. The standard error of the difference between two means was plus or minus 0.042. The difference between the two means was .200. This would mean that the difference between the two means was at least four and one-half times that of the standard error of the difference between the two means. The occurrence of an error by chance would be one in over 400 times. The reason for this fall could not be accurately determined, but it can be surmised that it is due to one of two things: (1) passing of true cholinesterase from the red cells to the myoneural junctions of the muscles of the gastrointestinal tract, or (2) as increased permeability of the cell. The former explanation seems more plausible at this time. In one case of nephritis in the nephrotic stage the patient had a normal serum cholinesterase with low albumin. This has been observed by other investigators,^{28, 29, 38, 30} and is thought to be due to the fact that albumin, being a smaller molecule, is excreted in the urine, while cholinesterase is withheld.

Other investigators have not reported the serum cholinesterase before and after operation. It was found that postoperatively, when a local or spinal anesthetic was used, there was a drop in serum cholinesterase. When a general anesthetic was used there was a rise in cholinesterase initially in all cases and a drop in four of the six cases. To explain the former, where apparently no liver damage would be involved, two patients were tested before and after administration of ACTH to see if stress was a factor. These people were found to have a decrease in serum cholinesterase after ACTH. It was thought that the drop postoperatively of patients having had local or spinal anesthesia was apparently due to stress. Where general anesthesia was used, the rise and then the fall of serum cholinesterase values were thought to be due to the fact that damage to liver cells may cause a release of cholinesterase from the liver, and then, when less is produced than preoperatively, there is a drop. Fall in serum cholinesterase took place in approximately 24 hours. In dogs poisoned with carbon tetra-

chloride, there is a rise of serum cholinesterase initially, and one to four days later there is a decrease, as is brought out by Brauer and Root.

CONCLUSIONS

1. The activity of serum cholinesterase is a useful liver function test that may be employed in the differential diagnosis of jaundice.
2. Serial determinations of serum cholinesterase values may be helpful in prognosis and in following recovery in cases of hepatitis.
3. Serum cholinesterase levels are low in condition with low serum albumin and in terminal and malignant diseases.
4. There is a drop in red blood cell cholinesterase after eating which is most probably due to passing of the enzyme from red blood cells to myoneural junctions of the musculature of the gastrointestinal tract.
5. Serum cholinesterase may drop during periods of stress.
6. The activity of the enzyme rises immediately postoperatively owing to flooding of the blood with cholinesterase from liver cells which are damaged, and later drops, when less than the normal amount of cholinesterase is produced in the liver.

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STUDIES OF THE HYPERLIPEMIA IN DIABETES AND OTHER DISORDERS *

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THE complexity of the fats and the fatlike substances and the technical difficulties of their extraction, purification and identification make the lipids seem to be an extremely formidable field of study. The usual chemical approach is to isolate a compound in pure form and then to determine its physical and chemical properties. About 15 years ago in the laboratory at St. Luke's Hospital Paul J. Hartsuch¹ attempted to prepare pure oleic acid from a mixture of saturated and unsaturated fatty acids. Distillation under reduced pressure, chilling to minus 15 to minus 25° C. of the fatty acid mixture diluted with an equal volume of 95 per cent ethyl alcohol or acetone, precipitation with barium and lead salts, and combinations of these procedures, with a final elaborate fractional distillation at 1 mm. Hg pressure, yielded a water-clear liquid that on testing consisted of 97.8 per cent pure oleic acid. It is reasonable to believe that the body tissues in the metabolism of the absorbed lipids do not separate into pure form and then specifically metabolize each one of the numerous lipids contained. Rather, complex mixtures of lipids within a wide range of chemical composition are absorbed and utilized.

All natural fats consist of mixed triglycerides, but each individual mixed triglyceride is usually chemically constituted according to a simple principle proposed by Hilditch,² and referred to as "even" or "widest distribution" of the fatty acid groups between the glycerol molecules. According to this principle, as soon as a given fatty acid forms about 35 per cent of the total fatty acids in a fat, it will occur at least once in every triglyceride molecule of fat, and no simple triglycerides containing three groups of the same fatty acid will occur until such acid forms nearly two thirds or more of the total fatty acids. Each fatty acid acts independently of the others in competing for union with glycerol, according to this general plan. In only two classes of animal fats does the formula fail to describe accurately the general glyceride structure of natural fats: (1) animal depot fats, which are unusually rich in mixed glycerides containing stearic groups, and (2) milk fats, in which the lower saturated acids from butyric to lauric are in appreciable amounts (13 per cent). The usual food fat during absorption in the intestinal tract³ is emulsified and partially hydrolyzed, and is liquid at the temperature of the body.

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The composition of the lipid mixtures in the blood introduces chemical considerations as well as one that is physical, the latter concerned with stability of emulsification, in which state the lipids are carried in transport through the blood and lymph for deposition in tissues or utilization by the cells. Instability of lipid dispersion, the separation from solution of the solids, and the unused residues of the lipid mixtures seem to be important pathogenic factors in causing injury of the tissues in disturbances of lipid metabolism.

The lipids of the blood are grouped into three main classes: (1) the fats, namely, the triglycerides of the saturated and the unsaturated fatty acids; (2) the fatlike substances, such as the sterols and their derivatives; and (3) the phosphatides, such as the cerebrosides and the ceramides. Systems for estimating the various chemical substances in a small amount of blood depend upon the production of an intense, specifically characteristic color which can be measured quantitatively and correlated with a standard. The cholesterol of the blood has been measured quantitatively in this way for many years. The other lipids had not been estimated in small amounts of blood because no comparable methods of analysis for these substances had been devised. Probably for this reason great emphasis has been placed on the cholesterol content of the blood and its variations in disease, without the knowledge that the other lipid fractions could fluctuate dependently and independently. Cholesterol chemically is a monatomic alcohol. It combines with a fatty acid to form esters, and these esters normally constitute 70 to 75 per cent of the total serum cholesterol. The fatty acids in these cholesterol ester compounds are probably contributed by the neutral fats. The neutral fat of the lipid fraction of the blood is glycerol-fatty acid esters. The mono amino phosphatides, lecithin and cephalin, are choline and cholamine phosphoric esters which have replaced, respectively, one of the three fatty acid radicals of glycerol. These diglycerol esters, lecithin and cephalin, are related chemically to neutral fat. According to Thannhauser,⁴ 70 to 90 per cent of the total phospholipids of the serum may be evaluated as lecithin.

These comments emphasize that the esterified fatty acids of the blood form a considerable amount of the total lipids. This fraction of the blood lipids has not been investigated in detail because systems of blood lipid analyses did not include a method for making these estimations colorimetrically with small quantities of blood. In 1949 Dr. Frederick Bauer published with me⁵ a method for the colorimetric determination of the total esterified fatty acids in human serums. The method is based upon the conversion of fatty acid esters into the corresponding hydroxamic acids by hydroxylamine hydrochloride and sodium hydroxide, and their subsequent conversion into colored ferric salts. The so-called fasting level of the serum esterified fatty acids in 102 normal human adults was found by this method to range between 7.0 and 12.6 mEq./L., with a mean average of 9.2 mEq./L.⁵ a range in keeping with values obtained by other methods.

With Lynn Carbonaro⁷ this method was then used in an investigation of the variations in the level of the esterified fatty acids of the serum in healthy human adults and in diabetics after the ingestion of a standard meal of fat. Others have studied the lipid content of the blood following a test meal of fat. Man and Gildea⁸ observed a notable increase of the serum fatty acids after a fat test meal of unsalted butter and 40 per cent cream in the ratio of 3.5 to 4 gm. fat per kilogram of body weight. The increase ranged between 34 and 133 per cent, and the maximal level in the blood was reached in four to six hours. Even with a standard meal containing 0.5 to 1 gm. of fat per kilogram of body weight, the postprandial elevation ranged between 21 and 40 per cent. In the morning, about 14 hours after the evening meal of the day before, Miss Carbonaro and I gave to healthy adults and to diabetics under control a fat meal consisting of 36 per cent cream (largest portion), unsalted butter, water-packed fruit, gluten bread and coffee but no sugar, in the amounts of 2 or 3 gm. of fat per kilogram of body weight. At 8:00 a.m. the first sample of blood was taken, and between 8:00 and 9:00 a.m. the test meal was eaten. Seven samples of blood were drawn thereafter at intervals of one hour while the subject was at rest. The serum fatty acids in healthy human adults increased appreciably following a meal containing 2 or 3 gm. of fat per kilogram of body weight. The increment of increase was not the same, nor was it reached within the same time in the various persons tested; also, the increase was greater in the same person with the 3 gm. per kilogram ratio than with the 2 gm. ratio. After the maximal level of increase was reached, the serum fatty acids declined toward the initial level. Among the 28 tests completed, the maximal level of the serum fatty acids in 10 was reached in three hours, in another 10 in four hours, in four by the second hour, in three by the fifth hour, and in one within one hour. The initial serum fatty acid levels found in 28 tests on 21 human adults ranged between 7.1 and 10.8 mEq./L., and averaged 8.8. The initial fatty acid value was used as reference in computing the individual percentages of increase. Starvation would, of course, lower the initial value. The total cholesterol values of the serums determined with each analysis for esterified fatty acids were remarkably unchanged during the postprandial hyperlipemia, fluctuating within a narrow range slightly more or even less than the value of the fasting level. Accordingly, the cholesterol content of the serum is not an index of the total lipid content of the blood in the postprandial hyperlipemia.

In 13 clinically mild diabetics, with or without insulin control, the initial fasting level of the serum fatty acids was in the high range for healthy adults, and the postprandial (fat meal) peak level ranged into the highest values observed in the normal group. Moreover, the maximal level of the serum fatty acids in the postprandial lipemia of persons with mild diabetes was attained later than in the normal adults. The duration of the postprandial lipemia in the diabetic, therefore, was longer than in the normal human adult. The cholesterol content of the serum in these mild diabetics did not

vary significantly from the initial level. Eight patients with severe diabetes (all using insulin) had a similar but more pronounced increase of the serum fatty acids following the fat test meal. The initial serum fatty acid content in these was above the highest initial values observed in the normal group and even exceeded the maximal postprandial level of several, was attained late, and was several or even many times that of the healthy group. In diabetes, accordingly, the postprandial phase of lipemia is prolonged and the percentage increase over the initial, also elevated level, is large. The cholesterol analyses in each of these fat tolerance tests gave no indication of the postprandial hyperlipemia which the quantitative analyses of the serum esterified fatty acids disclosed. The sugar level of the blood during the time of the tests did not vary with the increase in the serum fatty acids.

The index used for many years to guide the management of diabetes mellitus was the efficacy with which the excretion of glucose in the urine could be controlled. When methods for measuring the glucose content of the blood were devised, the maintenance of the sugar of the blood at normal levels became the objective. The metabolism of both carbohydrates and fats in diabetes mellitus is abnormal, and the blood of a patient with severe diabetes is hyperlipemic. The pattern of the hyperlipemias in diabetes mellitus has not been investigated because systems of blood analyses have not included methods for the fractional estimation of the lipids other than cholesterol in small amounts of blood comparable in precision to those with which the glucose content of the blood is measured. Clinicians for many years have taken the cholesterol level of the blood as an index of the entire lipid fraction. However, analyses of the hyperlipemic blood of animals made diabetic by removal of the pancreas and similar examinations of the blood lipids of human diabetes have disclosed that the triglyceride fraction in diabetic lipemia is increased most, while the cholesterol and phospholipid fractions are increased but slightly or not at all.

The need for careful regulation of the diet and insulin control of the diabetic is now in dispute among clinicians. The one group holds that the blood sugar of the diabetic should be maintained as near to the normal level as is possible by dietary regulation and insulin control. The other group argues that the diabetic's hyperglycemia and glycosuria do not make him more susceptible to infection, coma or vascular disease; hence, he should have a liberal diet and protamine insulin as prescribed. Current views applied to the marked incidence of atherosclerosis among diabetics suggest a direct causal relation between the hyperlipemia in diabetes mellitus and the evolution of the arterial disease in these patients.

Since lipemias, specifically those of diabetes mellitus, have this significance, Brendan P. Phibbs and Lynn Carbonaro made with me⁹ a quantitative study of the lipids of the blood in diabetes under conditions of blood sugar control and when the patients are hyperglycemic. These studies were made during (1) the hyperglycemia following withholding of insulin; (2) fat tolerance tests with the patient normoglycemic and with the patient

hyperglycemic; (3) fluctuations of blood sugar in a diabetic difficult to control; and (4) modifications of blood sugar by insulin or dietary control, or both.

The results demonstrated clearly that hyperglycemia in diabetic patients is associated with a marked elevation of the esterified fatty acids of the blood. When the hyperglycemic blood of a diabetic becomes normoglycemic through diet or insulin control, or both, the lipid fraction also returns to the normal range. When a standard fat tolerance test is made in a hyperglycemic diabetic, each individual fatty acid value determined during the test period is much higher and apparently in proportion to the degree of hyperglycemia than is the corresponding value in the test period when the fat tolerance examination is made with the blood normoglycemic. The cholesterol of the blood determined simultaneously with these analyses remained unchanged. These observations provide significant information

TABLE I

1953	Total Esterified Fatty Acids mEq./L.	Cholesterol			Fatty Acids	Phospholipids		Neutral Fat	Sugar mg. %	Total N.F.N. mg. %
		Total mg. %	Free mg. %	Ester mg. %	mEq./L.	mg. %	Fatty Acids mEq./L.	Fatty Acids mEq./L.		
3-23	98.8	550	236	314	8.1	26.2	15.2	75.5	600+	100
3-25	63.6	572				24.0				104
3-27	54.4	509				18.8			253	84
3-28	49.4	450				21.2			454	84
3-30	23.2	323	143	180	4.6	14.0	8.1	10.5	188	84
4-3	19.8	190	69	121	3.1	9.8	5.6	11.1	206	40
4-15	15.3	130				8.8			194	28
4-27	15.0	148	42	106	2.7	9.1	5.2	7.1	112	23
8-1	13.4	201	55	146	3.77	12.1	7.0	2.6		

in deciding whether the blood sugar of a diabetic should or should not be maintained within the normal range. The data used to evaluate this relation, so far, have been statistical.

Analyses of the blood lipids in a patient admitted to the hospital in diabetic coma afforded the opportunity to examine ratio relations between the neutral fat, the phospholipid and the free and total cholesterol fractions of the blood lipids during and following recovery. These results disclose a marked hyperlipemia during the coma of this diabetic patient in which all fractions of the lipids were increased. The neutral fat fraction, however, represented the largest amount of the total esterified fatty acids. The total cholesterol during coma was increased; the cholesterol ester fraction of the total decreased to approximately 57 per cent, but later, with the decrease of total cholesterol, the percentage rose to 72. Similar changes occurred in the phospholipid.

Hyperglycemia in the human diabetic is associated with a hyperlipemia the intensity of which seems to approximate the severity of the hypergly-

emia. In these hyperlipemias of diabetes mellitus, the triglyceride fraction of the blood lipids is increased the most, the cholesterol and the phosphatides slightly or not at all except in the conditions of diabetic coma. When the hyperglycemic blood of a diabetic becomes normoglycemic through diet or insulin control, or both, the esterified fatty acids of the blood return to the high normal ranges. The values of the esterified fatty acids of the blood obtained during a fat tolerance test are much higher when the diabetic is hyperglycemic than the corresponding values obtained when the test is made while the blood is normoglycemic. The demonstration that hyperglycemia in a diabetic is associated with a parallel and apparently proportional hyperlipemia emphasizes that the maintenance of the blood sugar of these patients at normal levels also controls the lipid content of the blood. According to current views on the rôle of the lipids in the evolution of atherosclerosis, the maintenance of the blood lipids at or near the high normal range probably is significant in delaying the evolution of degenerative vascular disorders in diabetics.

Hyperlipemia occurs in various other clinical and experimentally induced disorders. Among these are idiopathic hyperlipemia, the hyperlipemia of nephrosis, and the hyperlipemia produced in lower animals, such as the rabbit, following nephrotoxic agents,^{10,11} ligation of the renal blood vessels¹² and with alloxan poisoning. Unpublished studies in liver disease also indicate variations in the amount of the esterified fats in the blood and variations in the proportion of the various constituents in the lipid fraction.

GENERAL COMMENTS

The lipids of the blood are transported as emulsified particles of mixed chemical composition. As with any emulsion, the size of these particles varies, and chemical analyses should demonstrate beyond doubt that size variation in such a system is related to differences in the chemical composition of the various lipid particles. The emulsified lipids are a mixture of neutral fats, phospholipids, cholesterol esters, and cholesterol liquid at body temperature. The liquid neutral fats such as olein are the solvents holding in solution aliquots of lipids such as cholesterol, the stearic and palmitic acid esters of cholesterol, and the phospholipids stearin and palmitin all of which are solid at body temperature. The neutral fats, the phospholipids and the cholesterol esters contain fatty acids. Studies of the blood lipids indicate convincingly that the distribution of the esterified fatty acids in the various lipid fractions is important in order to determine abnormal patterns. This is the direction of further studies, with the hope that diagnostic patterns will be found. The composition of the emulsified lipid mixture of the blood can be likened to a solvent and its solutes. At the one extreme the solvent is in excess, as with the postprandial hyperlipemia, the early phases of idiopathic hyperlipemia, and in most forms of the diabetic hyperlipemia. At the other extreme the solutes approach

the supersaturation level, as with experimental cholesterol feeding in rabbits and the resultant atherosclerosis, and probably in the diabetic with xanthomatosis. There is evidence of a reversal process in the latter condition, that is, a reabsorption of the deposited lipids when the hyperlipemia of the blood is corrected. In some experiments in rabbits given forced feedings of cream (solvent), the animals developed a serious metabolic disturbance and died acutely. The livers had marked fatty changes. Persistence of the imbalance when a solute is in excess, as with cholesterol feeding in rabbits, leads not to an acute death but to a wasting disorder associated with large deposits of cholesterol in the lining of the aorta and in many tissues of the body.

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SPONTANEOUS RUPTURE OF ESOPHAGUS *

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SPONTANEOUS rupture of the esophagus, although rare, is a long recognized and well established clinical entity. Having recently observed three cases, we became interested in studying the mechanism by which this phenomenon is produced. We attempted to reproduce esophageal rupture by means of hydrostatic pressure applied intraluminally to the esophagi of cadavers. Use of a radiopaque suspension within the esophagus enabled us to study the changes in outline of the esophagus by fluoroscopy. Linear ruptures of the esophagus similar to those which occur spontaneously were consistently produced in the lower left lateral aspect.

There are well documented series of experimentally produced esophageal ruptures. MacKenzie¹ in 1884 tied the distal end of esophagi removed from cadavers and introduced water under pressure into their proximal end. At an average pressure of 7 pounds per square inch tears were produced which were very similar in appearance to those occurring in cases of spontaneous rupture. In all but one of 18 experiments the tears occurred just above the cardia, and varied from 1 to 5 cm. in length. MacKenzie observed that, during rupture, the mucosa and the muscle coat gave way together in more than half of the cases. In the remainder, the mucosa bulged out in a hernia-like sac between the separated muscle fibers before giving way. In all cases the defect in the mucosa was smaller than that in the muscularis. He concluded that rupture by direct pressure within the esophagus always takes place in a longitudinal direction, that it never occurs in the upper part of the esophagus, and that the mucous membrane appears to offer greater resistance to strain than the muscularis. Mackler² repeated MacKenzie's experiments and confirmed his results.

Duval³ and Burt,³ independently, recognized that the rapidity of increase in the intraluminal pressure, rather than the amount of pressure, is the important factor in producing esophageal rupture.

Kinsella, Morse and Hertzog⁴ have demonstrated similar rupture by the slow application of pneumatic pressure to esophagi of cadavers.

By applying pressure from below to the esophagus in situ, we have attempted to reproduce the process, as it occurs spontaneously, more closely than was done in the above experiments. A tube was inserted in the stomach and tied in place below the cardia, leaving the esophagus and chest intact. Although there was probably some weakening of the esophagus due to postmortem autolysis, the buttressing effect of the contiguous supporting

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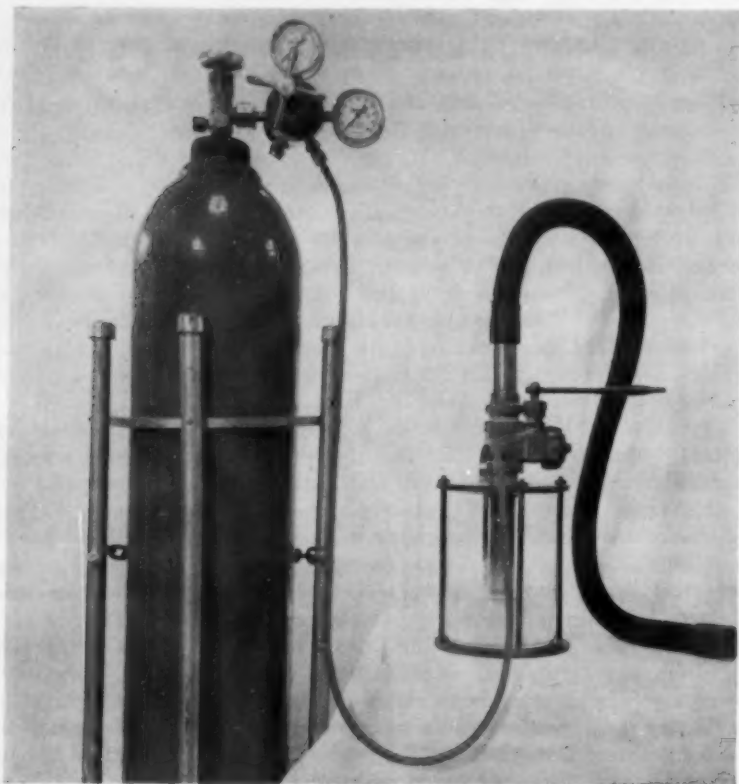


FIG. 1.

structures was retained. Hydrostatic pressure was then produced through the tube by the application of oxygen under pressure against a barium suspension. The pump (figure 1) used to produce this pressure consisted of a glass jar 20 cm. in height and 14 cm. in diameter. The jar was covered by an iron plate with a rubber fitting. A copper tube was inserted through the center of the iron plate, almost reaching the base of the jar. Liquid contrast material (barium sulfate suspension) was placed in the jar, and the pressure for the ejection of the fluid was furnished by passing oxygen from a high pressure tank through a small hole in the iron plate. Attached to the tank was a gauge which registered the applied pressure in pounds per square inch.

The copper tube as it emerged from the cover of the glass jar was attached to an eccentric balanced valve which opened the entire lumen with one sudden snap. The valve in turn was connected to a rubber tube. The

inner transverse diameter of the copper tube was 3.2 cm., allowing the instantaneous ejection of 1 to 3 quarts of liquid into the rubber tube, which was of similar diameter. This rubber tube was 120 cm. in length, and the distal end of the tube was tied into the upper third of the stomach about 5 cm. below the cardia.

The clinical history of the deceased was carefully checked to rule out any pathology in the stomach or esophagus. A midline incision was made on the cadaver to expose the stomach, which was then severed at the



FIG. 2.

junction of the middle and upper third. The end of the tube was attached to the proximal stump by circular ties.

To perform the experiment, the entire system was filled and two quarts of suspended contrast material were placed in the jar. In order to have a closed system, the cardia was clamped by hand. The pressure gauge was released and set at the selected pressure. The valve was opened quickly, and simultaneously the constriction of the cardia was released. Two representative experiments were performed and observed under fluoroscopy to study the changes in outline of the esophagus. X-rays were taken at several stages of the procedure. In three additional experiments, the technic was the same except that there was no x-ray control.

In a representative experiment, the esophagus of a 73 year old female cadaver was ruptured three hours post mortem. No evidence of gastrointestinal pathology was noted prior to the procedure. When the contrast material was injected at a pressure of 1.5 pounds per square inch, the fluoroscope showed bulging of the lower end of the esophagus, just above

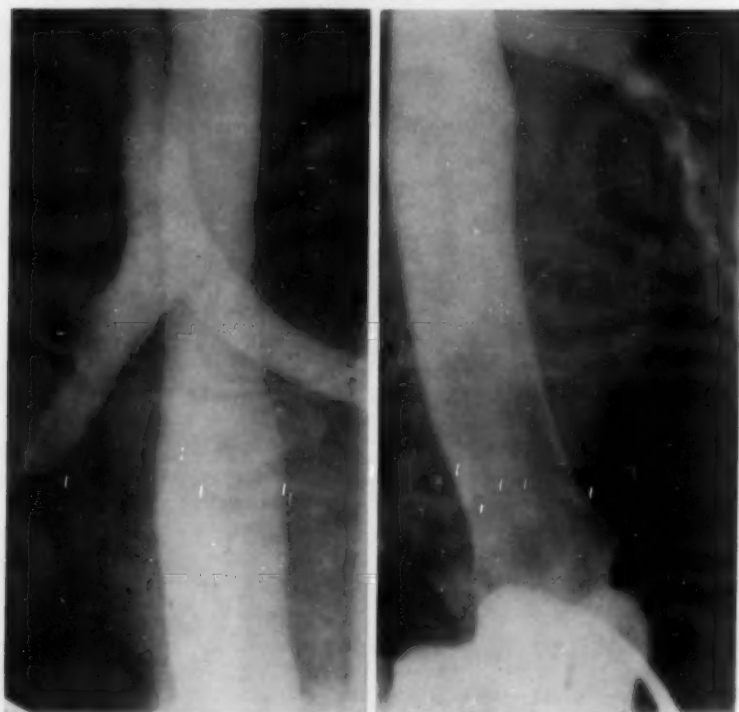


FIG. 3.

the cardia (figure 2). In order to delineate the relationship of the esophagus to the left pulmonary root, the bronchial tree was filled, without pressure, with barium sulfate suspension. The stream of contrast material definitely narrowed at the level of the left pulmonary root, where the left bronchus



FIG. 4.

not cause rupture. When the mouth was closed, rupture of the esophagus occurred at 6 pounds per square inch.

DISCUSSION

Hydrodynamic forces are accepted by most observers as the factor responsible for spontaneous rupture of the esophagus. Mackler² concluded that "the sudden rise in the intra-abdominal pressure during vomiting or produced by retching, as well as by other means, causes compression of the stomach, which results in violent ejection of gastric contents into the esophagus, causing rise in the intraluminal pressure which may be sufficient to overcome the tensile strength of the wall, which then bursts." The necessary intra-abdominal pressure is exerted by the abdominal muscles and the diaphragm. The incompressible fluid serves as a transmitting force, finding its way from the full stomach into the esophagus. The large amount of fluid cannot be expelled from the esophagus at the same rate as it is received from the stomach. Consequently, the esophagus distends under great pressure, much as though it were a blind tube, and rupture occurs at the weakest point.

Quigley and Brody⁵ deduced equations based on physical principles suggesting that the potential bursting tension of a hollow organ resulting from application of pressure within the cavity is directly proportional to the intraluminal pressure and the size of the viscus, and is dependent on the shape of the viscus. In the case of cylindrical organs the circumferential bursting tension is $T_{\text{circ}} = P \times r$, while the longitudinal bursting tension is $T_{\text{long}} = P \times r/2$. According to these formulae, less tension is required to cause rupture in a longitudinal than in a circular direction. This is borne out by the findings in the experimental and spontaneous ruptures of the esophagus.

We know of no observation in humans of muscular phenomena concerned in forcible regurgitation, except for belching which has been studied under fluoroscopy with the mucosa coated with barium. Templeton⁶ noted that under such conditions the cardiac incisura disappeared and the abdominal portion of the esophagus was absorbed into the gastric lumen. Joannides⁷ similarly noted that during conscious belching, contraction of the costal portion and relaxation of the vertebral portion of the diaphragm occurred, accompanied by squeezing of the stomach by contracted abdominal muscles. He also noted an hour-glass appearance of the stomach due to constriction in its midportion. It may be assumed that similar muscle forces are present in the act of vomiting, which would tend to build up intraluminal pressure.

The history of patients who have had spontaneous esophageal rupture emphasizes the importance of hydrostatic pressure in producing this accident. In a series reported by Ware, Shnider and Davis,⁸ 75 out of 86 cases had a history of vomiting or retching. In those patients who did not have

vomiting, there were other causes for increased intra-abdominal pressure, such as labor of childbirth,⁹ weight lifting¹⁰ or defecation.¹¹

Anderson¹² and Mackler² are in agreement that a full stomach is necessary if rupture of the esophagus is to take place by the transmitted force of the suddenly ejected gastric contents. With a full stomach, the pressure cannot be released by distention of the lumen of the stomach. We have, however, seen clinical exceptions. In the series of Ware and others,⁸ out of 86 cases 42 had no history of ingestion of a large meal or alcohol with its associated large fluid volume. The poor history of these patients, because of their prostrate condition, may account for this lack of information.

The ability of the stomach to receive relatively large quantities of material without developing significant rise in the intraluminal pressure has been demonstrated in experimental animals.⁵ This "receptive relaxation" may be upset by an unusually large intake. The development of excessive intraluminal pressure may lead to a series of events, including increased secretion, general inhibition of motility of the gastrointestinal tract, and vomiting, which may result in rupture of the esophagus.

It is believed that the excitability of the vomiting center is raised in the presence of dehydration, inadequate carbohydrate intake and anoxia of the medulla.¹³ In the case of alcoholism, vomiting frequently occurs and, abetted by starvation and dehydration, a vicious cycle may be established. The degree of vomiting may be so excessive as to cause fatigue of the vomiting center. Under such circumstances there may be neuromuscular incoordination causing sphincter spasm and functional obstruction of the esophagus.¹⁴ This physiopathologic state may also exist in cases of vomiting in confused mental states or in coma.

Russell¹⁵ and Mackler² pointed out the importance of functional obstruction due to spasm of the cricopharyngeus muscle. Such spasm is promoted by regurgitated acidic gastric contents to this region. The functional sphincter obstruction in the face of the generating forces from below may be responsible, according to Mackler, for the momentary development of sufficient pent-up pressure to burst the esophagus. As we have demonstrated in one of our experiments, it is our impression that the necessary bursting pressure is less in the presence of obstruction at the upper end of the esophagus.

Although the mechanism of rupture is well explained on a mechanical basis, there are other important factors to be considered. There are anatomic features which favor rupture in the lower segment of the esophagus.¹⁶ It is significant that the muscle fibers at the lower end of the esophagus terminate in a conical fashion and are tapering and thinned out. In addition, in this region there is inherent weakness at the site of entrance of vessels and nerves into the musculature, and segmental defects are found sometimes in the circular muscle layer. The observed angulation formed between the abdominal and thoracic esophagus is also significant because it may favor obstruction with resultant increased intraluminal pressure.

In the lower esophagus, arrangements of muscle fibers are spiral and elliptical, and the thickness of the inner muscle layer is believed to be less than elsewhere. This also predisposes to the development of pulsion diverticula after the mucosa herniates through the weak points in the inner muscle of the lower esophagus.¹⁷

There have been reported cases of rupture of the esophagus accidentally produced in living people by pneumatic pressure.¹⁸ In one case, the full force of compressed air in the inner tube of a tire was released, after a blowout, to the open mouth of a child and caused a rupture of the esophagus 6 cm. above the cardia in the posterior aspect.¹⁹ Thus, rupture of the esophagus occurs usually in the same part, whether spontaneous, accidental or experimental.

Wangensteen¹² considers acid peptic digestion as the primary etiologic factor for rupture of the esophagus. He based his theory on perforations produced in animal experiments. However, in humans, the role of acid pepsin in the actual initiation of esophageal ulceration is not firmly established. "Reflux esophagitis" may occur with normal acidity and be absent in patients with a high acid curve. Further, in cases of hiatus hernia acid reflux was found both with and without esophagitis. In a number of patients suffering with hiatus hernia and esophagitis it was not possible to demonstrate esophageal reflux.²¹ Brosch, as quoted by Gott,²² incubated a length of human esophagus in acidic peptic juice and was unable to demonstrate increased weakness of the wall to a bursting pressure. We do not believe that acid peptic digestion is the primary factor, but accept the fact that, in the presence of ulceration of the esophagus, regurgitated gastric juices may increase the esophagitis and weaken the wall of the organ.

It should be noted that the type of patient with a ruptured esophagus may have been prone to esophagitis. This may be associated with a pre-existing esophagitis due to the irritant action of excessive alcohol ingestion. Thus, Ware and others noted that 29 out of the 86 cases they studied had a history of alcoholism.

There is a significant incidence of peptic ulcers of the stomach or duodenum with rupture of the esophagus. Thus, in 27 cases who had rupture of the esophagus and an associated disease, there were eight duodenal and three gastric ulcers.⁸ In two of our autopsied cases there were chronic duodenal ulcers. The tendency to obstruction and vomiting of these patients may be predisposing factors.

SUMMARY

Rupture of esophagi performed in cadavers, with retrograde injection of contrast material under pressure and fluoroscopic control, allowed us to observe the sequence of events in the esophagus left intact in situ. The typical protrusion in the lower left lateral third of the organ was noted and the ruptured specimens were similar to those seen clinically or in other experimental series.

Hydrodynamic forces are responsible for spontaneous rupture, but the actual occurrence is most probably the result of a combination of several factors, including anatomic or acquired weakness of the wall, neuromuscular incoördination, chemical damage to the mucosa and general debility.

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A NEW TEST OF PANCREATIC FUNCTION BASED ON STARCH TOLERANCE*

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IN searching for a test of pancreatic function which would be useful in the diagnosis of chronic diseases of the pancreas, as well as practical under conditions of ordinary hospital and office practice, the authors explored the possibility of utilizing the digestive action of pancreatic juice on gelatin and on starch in the small intestine.

A gelatin tolerance test was first proposed by West, Wilson and Eyles¹ for the purpose of diagnosing cystic fibrosis of the pancreas in children. The test is based on the assumption that trypsin plays an important part in the hydrolysis of proteins, and that the rate of digestion of a protein meal can be estimated by the ensuing elevation of the amino acid nitrogen in the blood. These authors observed flat blood amino acid nitrogen curves after ingestion of casein and of gelatin, respectively, in seven and in two children with fibrocystic disease of the pancreas. When a casein hydrolysate or casein with pancreatin was administered to these children, a higher or even normal level of amino acid nitrogen in the blood was produced. Anfanger and Heavenrich² utilized the gelatin tolerance test in five patients with this disease and confirmed the findings of West et al. They suggested the use of a glycine tolerance test in children with low blood amino acid nitrogen curves during the gelatin test to rule out misleading results due to diseases associated with impaired intestinal absorption. More recently, Woiski³ reported similar observations with the gelatin test in four children with fibrocystic disease of the pancreas. The results of these investigators appear to be valid, although none of the reported series is large enough to permit statistical analysis.

In our experience the gelatin tolerance test, as will be detailed later, proved unreliable for the diagnosis of pancreatic disease in adults. It occurred to us that starch might be better than gelatin as a test material for our purpose since, because of the weak amylolytic properties of ptyalin, the short duration of its action, and the absence of amylolytic ferments in the succus entericus, the digestion of starch depends on pancreatic amylase to a much greater degree than the digestion of gelatin depends on trypsin. With these considerations in mind the starch tolerance test described below was devised.

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METHODS

Starch Tolerance Test: One hundred grams of "Soluble Starch" (prepared according to Lintner and marketed by Merck & Co., Inc.) are suspended in 150 c.c. of water by mixing with a spoon. Just before the test this suspension is poured into 300 c.c. of water which has just ceased boiling, and is thoroughly stirred. The patient eats the resulting gelatinous mass on a fasting stomach as soon as it has cooled sufficiently. Specimens of venous blood for sugar determinations⁴ are taken before, and 30 minutes, one hour, two hours and three hours after administration of the starch.

In attempting to make the starch more palatable we found that the addition of fresh lemon juice scarcely changed the taste and that a commercial lemon extract had a tendency to hydrolyze the starch and thus to interfere with the test. It was also found that if the starch is mixed with cold water and administered at this temperature, flat curves result even in normal subjects. If the suspension of starch is allowed to boil, even patients with severe pancreatic insufficiency have blood sugar curves within the normal limits, presumably because the starch is partially hydrolyzed by heat into a less complex carbohydrate (maltose), which is easily converted by the ferments of the succus entericus into glucose. Working out the proper preparation of the starch as described above was the only difficulty which had to be overcome in devising this test.

Patients with diseases of the pancreas, even in the absence of clinical diabetes mellitus, often have a reduced glucose tolerance which unavoidably increases the height of the blood sugar curve obtained after administration of starch. To arrive at the correct answer it is necessary to obtain, in addition, a glucose tolerance curve following ingestion of 100 gm. of glucose. The maximal rise in blood sugar during the glucose and the starch tolerance tests is determined by subtracting the value for the fasting blood sugar of each curve from that of the peak of the respective curves. Then, the extent to which the maximal rise in blood sugar after glucose exceeds that after starch is calculated in percentages and compared with the normal range obtained from patients without diseases of the pancreas.

Gelatin Tolerance Test: Fifty grams of Knox gelatine are dissolved in 250 c.c. of water and administered orally to the fasting patient. If desired, the gelatin can be flavored with lemon juice or lemon extract. Specimens of venous blood for determinations of amino acid nitrogen⁵ are taken before, and one hour, two hours, three hours and four hours after the ingestion of gelatin. The maximal rise of the amino acid nitrogen level in the blood during the test is determined by subtracting the value obtained from the fasting blood specimen from that of the peak of the curve. Since in patients with pancreatic diseases the utilization of amino acids is presumably normal, a control glycine tolerance test is not necessary. In cases where creatorrhea or steatorrhea is present, however, it is well to rule out impaired intestinal absorption of amino acids by comparing a blood amino acid nitrogen curve

obtained after oral administration of 50 gm. of glycine with the normal range as determined in control subjects without diseases known to be associated with decreased intestinal absorption.

CLINICAL MATERIAL

The clinical material for this study was obtained from the wards of the University of California Hospital and from the Gastrointestinal Clinic. All patients had a thorough work-up, including history, physical examinations, and laboratory and roentgenologic studies as indicated. The diagnosis was made in all cases by senior members of the faculty, almost always in consultation with members of the staff of the Gastrointestinal Clinic and without regard to the outcome of the starch and gelatin tolerance tests.

The starch tolerance test was performed on 27 control patients without pancreatic disease, approximately one-half of whom suffered from conditions

TABLE I
Results of Starch and Gelatin Tolerance Tests in Control Subjects

Diagnosis	Starch Test %	Gelatin Test mg.-%	Remarks
1 Anxiety neurosis	+39	—	Healed duodenal ulcer
2 Anxiety neurosis	+29	7.9	Laparotomy: healed duodenal ulcer
3 Anxiety neurosis	+17	6.2	Vague abdominal distress
4 Anxiety neurosis	+51	3.4	Vague abdominal distress
5 Anxiety neurosis	-54	3.1	Mild epigastric discomfort
6 Anxiety neurosis	+1	—	Epigastric pain. Laparotomy: negative
7 Anxiety neurosis	0	—	Spastic colon
8 Anxiety neurosis	+25	—	Vague abdominal pain
9 Anxiety neurosis	+31	—	
10 Anxiety neurosis	+23	—	Vague abdominal distress
11 Anxiety neurosis	+9	4.0	Vague abdominal distress
12 Radiculitis	+12	—	Abdominal pain (L.U.Q.) due to osteoarthritis of spine
13 Tabes dorsalis	+21	8.0	
14 Diabetes mellitus	+51	—	
15 Diabetes mellitus	+47	—	
16 Chronic cholecystitis with cholelithiasis	+7	3.9	Laparotomy
17 Chronic cholecystitis with cholelithiasis	+46	—	Laparotomy
18 Periodic cholangitis	0	—	Laparotomy
19 Post-cholecystectomy syn- drome	-16	—	
20 Post-cholecystectomy syn- drome	+49	—	
21 Duodenal ulcer	-43	5.8	
22 Duodenal ulcer	+34	4.8	
23 Chronic diarrhea	+36	12.2	Cause unknown
24 Chronic diarrhea	-18	2.9	Cause unknown
25 Chronic diarrhea	+38	—	Cause unknown
26 Chronic diarrhea	+17	—	Cause unknown
27 Chronic diarrhea	+20	—	Chronic alcoholism
28 Anxiety neurosis	—	4.5	
29 Anxiety neurosis	—	6.5	Vague abdominal pain
30 Anxiety neurosis	—	4.7	Vague abdominal pain

TABLE II
Results of Starch and Gelatin Tolerance Tests in
Patients with Chronic Pancreatic Disease

Diagnosis	Starch Test %	Gelatin Test mg. %	Remarks
1 Chronic pancreatitis	+109	3.6	Moderate calcinosis. Laparotomy
2 Chronic pancreatitis	+257	2.5	Extensive calcinosis. Clinical diabetes. Osteomalacia
3 Chronic pancreatitis	+287	6.6	Minimal calcinosis. Latent diabetes
4 Chronic pancreatitis	+389	—	Minimal calcinosis. Clinical diabetes
5 Chronic pancreatitis	+ 56	7.4	Minimal calcinosis
6 Chronic pancreatitis	+126	7.2	Latent diabetes. Laparotomy
7 Chronic pancreatitis	+191	—	Extensive calcinosis. Clinical diabetes. Laparotomy
8 Chronic pancreatitis	+154	3.3	Moderate calcinosis
9 Chronic pancreatitis	+419	1.3	Extensive calcinosis. Palpable pancreas. Clinical diabetes
10 Chronic pancreatitis	+110	—	High serum amylase 1 year ago
11 Chronic pancreatitis	+ 57	3.0	Latent diabetes. Steatorrhea
12 Chronic pancreatitis	+481	—	Steatorrhea
13 Chronic pancreatitis	+246	2.4	Latent diabetes. Steatorrhea
14 Cystic fibrosis	+287	2.8	Latent diabetes. Steatorrhea. Bronchiectasis
15 Carcinoma of pancreas	+285	3.1	Diffuse tumor. Latent diabetes
16 Carcinoma of pancreas	+227	1.6	Diffuse tumor
17 Carcinoma of pancreas	+590	1.8	Diffuse tumor involving stomach and duodenum
18 Carcinoma of pancreas	+377	2.7	Diffuse tumor
19 Carcinoma of pancreas	+230	3.2	Diffuse tumor; widespread involvement of peritoneum. Clinical diabetes
20 Penetrating duodenal ulcer with chronic pancreatitis	+154	—	Latent diabetes. Laparotomy
21 Penetrating duodenal ulcer with chronic pancreatitis	+ 82	—	Latent diabetes. Laparotomy
22 Penetrating duodenal ulcer with chronic pancreatitis	+193	3.9	Clinical diabetes
23 Penetrating duodenal ulcer with chronic pancreatitis	+177	—	—

TABLE III
Results of Starch and Gelatin Tolerance Tests in Patients with
Suspected Chronic Pancreatitis

	Starch Test %	Gelatin Test mg. %	Remarks
1	+112	3.4	Recurrent severe upper abdominal pain. Clinical diabetes
2	+124	—	Recurrent upper abdominal pain. Weight loss
3	+ 33	5.1	Recurrent moderate epigastric pain. ? Minimal calcinosis. Latent diabetes
4	+ 89	6.1	Recurrent mild epigastric pain. ? Minimal calcinosis. Latent diabetes
5	+ 65	—	Recurrent epigastric pain. Clinical diabetes
6	+216	—	Recurrent epigastric pain. Cholecystitis with cholelithiasis
7	+123	3.2	Recurrent severe epigastric pain
8	+ 99	4.4	Recurrent epigastric pain. Latent diabetes
9	+189	4.6	Recurrent severe epigastric pain
10	+ 71	3.1	Epigastric pain. Weight loss

such as diabetes mellitus, chronic diarrhea, etc., which theoretically might interfere with the validity of the test (table 1). This test was also done on 36 patients in whom pancreatic disease was diagnosed or suspected. This group consisted of 23 patients with chronic pancreatic disease (table 2), 10 patients with suspected diseases of the pancreas (table 3), one patient with acute pancreatitis, and two patients with partial resection of the pancreas.

The gelatin tolerance test was performed on 15 control subjects (table 1) and on 28 of the patients in whom pancreatic disease was diagnosed or suspected (tables 2 and 3), who had been subjected to the starch tolerance test.

RESULTS

I. Starch Tolerance Test: The mean blood sugar curves after administration of glucose and of starch in control subjects and in patients with chronic pancreatic disease are shown in figure 1. The mean results of the starch tolerance test in controls and in patients with suspected and with diagnosed chronic pancreatic disease are given in figure 2A. The results of the individual starch tolerance tests in the same groups are shown graphically in figure 3.

A. Range of Normalcy: The results of the starch tolerance test in the control group ranged from -54% to $+51\%$, with a mean of $+13.9$ and a standard deviation of 28.2. From these figures the normal range in our series can be determined by using an interval of two sigma from the mean of patients without pancreatic disease—a statistical formula often employed

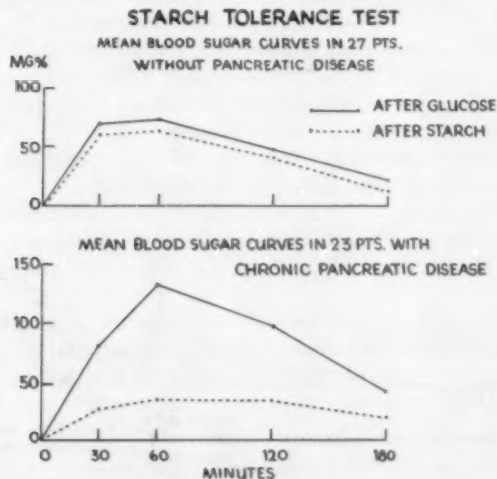


FIG. 1.

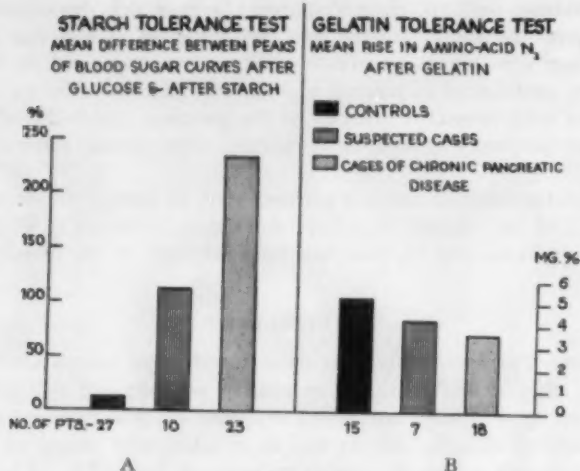


FIG. 2.

for biological procedures: Normal range = mean $\pm 2 \times$ standard deviation = $13.9 \pm 2(28.2) = -42.5$ to $+70.3$. Of these, only the upper limit of $+70\%$ concerns us here.

It can be seen from figure 3 that the results of all starch tolerance tests performed in patients without pancreatic disease are well below this upper limit. As an added precaution, until greater numbers of patients are tested

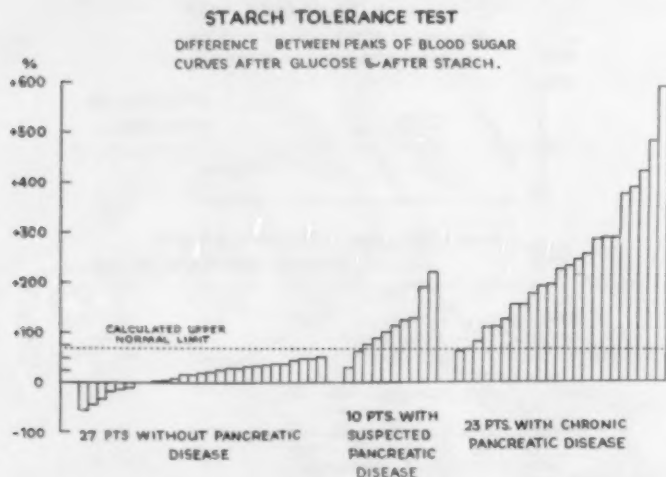


FIG. 3.

and until wider experience with the interpretation of this test is acquired, it is recommended that the results falling between +70% and +100% be considered "borderline," and that only values above the +100% level ($= \text{mean} + 3 \times \text{standard deviation}$) be interpreted as definitely abnormal.

B. Patients with Diseases of the Pancreas:

Chronic pancreatic disease: Of the 23 patients in this group, 14 were diagnosed as having chronic pancreatitis, with diabetes* in nine cases, pancreatic calcinosis in seven cases, and steatorrhea in four cases. The starch tolerance test gave positive results in all but two of these patients, in whom it was within the upper limit of normal. This group also included five patients with diffuse carcinoma of the pancreas proved by operation. Two of these patients had diabetes but none was jaundiced. The results of the starch tolerance test were markedly positive in all five cases. The remaining four patients in this group were suffering from a duodenal ulcer which had penetrated into the pancreas, with chronic pancreatitis. Three of the patients had diabetes. In these patients results of the starch tolerance test were positive in three cases and "borderline" in one.

Suspected pancreatic disease: This group consisted of 10 patients. In eight of these, chronic pancreatitis was suspected on the basis of clinical manifestations, which, however, were not sufficiently well defined to warrant a positive diagnosis. Three of them had diabetes. The outcome of the starch tolerance test was positive in six of these eight patients, "borderline" in one case, and within the upper limit of normal in one case. The two additional patients manifested questionable abdominal calcifications in a location compatible with the pancreas, diabetes, and rather vague abdominal distress. In one of these patients the results of the starch tolerance test were "borderline" and in the other, normal.

Acute pancreatitis: Only one patient with acute pancreatitis came to our attention during the course of this study. The low incidence of this disease in our series is explained by the fact that the University of California Hospital functions chiefly as a diagnostic center, with a long waiting list and few emergency admissions. The criteria for diagnosis in this patient were a clinical picture of an "acute abdomen" and a blood amylase value of 536 units. This patient also had latent diabetes. No operative evidence was available, since it is our policy to treat acute pancreatitis by medical measures. The outcome of the starch tolerance test in this patient was "borderline" (+80%).

Partial resection of the pancreas: In two patients who had undergone partial resection of the pancreas, one of whom had latent diabetes, results of the starch tolerance test were normal (+13% and +40%). The test was performed two weeks after operation in one case and one year later in the other.

* Designated in the tables as "clinical" and "latent," depending on whether the fasting blood sugar was over or under 100 mg. per cent. For either classification the blood sugar curve had to exceed 200 mg. per cent within the first two hours of the glucose tolerance test.

II. Gelatin Tolerance Test: The mean rise in blood amino acid nitrogen after gelatin in control subjects and in patients with suspected and with diagnosed chronic pancreatic disease is given in figure 2B. The results of the individual gelatin tolerance tests in the same groups are shown graphically in figure 4.

From figure 2B it is seen that the mean rise of blood amino acid nitrogen is slightly lower in patients with suspected diseases of the pancreas than in the control subjects, and that it is still lower in the patients diagnosed as having chronic pancreatic disease. This trend is continued in the patients with carcinoma of the pancreas (table 2), who have the lowest rise in the blood amino acid nitrogen of the four groups, and who as a group also show the greatest impairment of starch digestion.

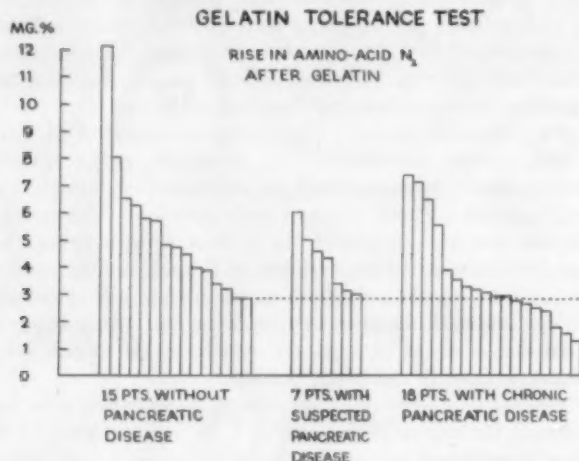


FIG. 4.

Figure 4 shows that the individual rise of blood amino acid nitrogen in 11 of 18 patients with chronic pancreatic disease and in all seven patients with suspected pancreatic disease was above the lowest rise in the control group. Furthermore, contrary to the observations of West et al.,¹ there was no delay in the rise of the blood amino acid nitrogen during the test in the two abnormal groups as compared to the control group.

The maximal rise in individual blood amino acid nitrogen curves of the control group ranged from 2.9 to 12.0 mg.%, with a mean of 5.2 mg.% and a standard deviation of 2.38. Applying the previously used statistical formula to the calculation of the normal range of the gelatin tolerance test we get: normal range = $5.2 \pm (2.38) = 0.4$ to 10.0. This means that the outcome of the gelatin tolerance tests in all patients of both abnormal groups was within the normal range.

As a check on the remote possibility that impairment of the ability to utilize glycine in patients with pancreatic disease might mask a failure of their blood amino acid nitrogen to rise normally, a glycine tolerance test was performed in several of these patients. The maximal rise in the blood amino acid nitrogen curves after glycine was determined by subtracting the value of the fasting specimen from that of the peak of the curve. Then, the extent to which the maximal rise in blood amino acid nitrogen after glycine exceeded that after gelatin was calculated in percentages and compared with the normal range found in patients without pancreatic disease. This procedure was carried out in six control subjects and in five patients suspected of or diagnosed as having chronic pancreatitis. In only one of the abnormal cases did the obtained figure exceed the range of the controls, and thus suggest the possibility of impaired utilization of glycine.

In two patients suffering from chronic pancreatitis with steatorrhea, the glycine tolerance test was used to rule out impaired intestinal absorption. In both cases the peak of the blood amino acid nitrogen curve after glycine (4.8 and 16.0 mg.%) was in the range obtained from six patients without pancreatic disease (3.6 to 16.0 mg.%, with a mean of 4.6 mg.%).

DISCUSSION

The much wider spread between the mean blood sugar curves after administration of glucose and of starch in our patients with chronic pancreatic disease than in our control subjects (figure 1) indicates that the basis of the starch tolerance test is sound. The difference between the results of the starch tolerance test in patients with and without chronic pancreatic disease was made even more significant by expressing the result of the test as a difference between the maximal rise of the blood sugar curves (figure 2A), rather than as a difference between surface areas under the respective curves obtained by planimetric measurements.

In a discussion of the significance of "averages" in appraising pancreatic function tests, Elman and Wheat⁶ aptly wrote: "The average figure in this type of observation is often meaningless unless analyzed statistically. To put the matter more simply, if the abnormal values are all below the lowest normal range, then the measurements would be significant. However, if there is considerable overlap among the highest values of the abnormal group and the lowest values of the normal group, it would be inaccurate, and even misleading, to compare averages." As seen from the results of the starch tolerance test in individual patients (figure 3), there is no overlap between the values for control subjects and those for patients in the group with chronic pancreatic disease. Furthermore, one can use the higher statistically calculated limit of normal (+70%) instead of the highest normal range (+51%), and even consider the zone between +70% and +100% as "borderline," as suggested under "Range of Normalcy," and

still find that the results of the starch tolerance test were abnormally high in 20 of 23 patients with chronic pancreatic disease.

Finally, statistical analysis of the above data shows that the difference between the control group and the group of patients with chronic pancreatic disease is highly significant, with P (probability factor) $= < 0.01$. This does not mean, however, that in an occasional patient with proved chronic pancreatic disease results of the starch tolerance test will not be normal. This aspect of clinical function tests is well known, and must be expected in the use of a pancreatic function test, the normal limits of which are calculated by adding an interval of two sigma to the mean obtained from control subjects without pancreatic disease. However, such predictable exceptions do not significantly impair the value of this test for the diagnosis of pancreatic disease.

The diagnoses in our group of control subjects (table 1), in addition to anxiety neurosis associated with functional indigestion, included diabetes mellitus, chronic cholecystitis with cholelithiasis (one patient had attacks of typical gall-stone colic), cholangitis, post-cholecystectomy syndrome, chronic diarrhea and duodenal ulcer. None of these diseases showed any evidence of interfering with the normal digestion of starch as indicated by the starch tolerance test. One additional patient (not listed in table 1) with the post-gastrectomy "dumping syndrome" but no clinical evidence of pancreatic disease, who had a blood sugar of only 27 mg.% in the two hour reading of the glucose tolerance test, exhibited a markedly positive response to the starch tolerance test (+190%). This finding may be attributed either to a precipitate emptying of the glucose solution into the small intestine, with consequent abnormally rapid absorption of this sugar,⁷ or to interference of the altered anatomic relations in the digestive tract with hydrolysis of starch. Pending further experience with the starch tolerance test in the "dumping syndrome," a positive response to the test in patients with this condition cannot be relied on as evidence of pancreatic insufficiency.

In the group of patients with chronic pancreatic disease as a whole, the starch tolerance test was positive in 87% of cases; these results were used above to establish the validity of the test. In the patients with chronic pancreatitis, the outcome of the test was positive in 86% of cases. In this connection, the authors wish to emphasize that the "accuracy" of this test, as of most clinical function tests, depends to a considerable extent on the criteria used for the selection of cases. It is apparent that stricter criteria lead to the choice of more severe cases, which results in greater "accuracy" of the test. For instance, if the mandatory criteria for diagnosis of chronic pancreatitis in every case were characteristic epigastric pain, frank diabetes, diarrhea with steatorrhea and creatorrhea, and calcinosis of the pancreas, the "accuracy" of any useful pancreatic function test would be almost 100%. Obviously, such strict criteria would also eliminate the necessity for pancreatic function tests. As some indication of the severity of the disease in the patients included in our group, the incidence of clinical

and of latent diabetes was 64%, of calcinosis of the pancreas, 50%, and of steatorrhea, 29%.

In the patients with suspected chronic pancreatitis in whom the clinical evidence was insufficient to make a positive diagnosis, the starch tolerance test was positive in 60% of cases. The uncertainty of diagnosis and the lesser degree of involvement of the pancreas in this group are demonstrated by the decreased incidence of diabetes (50%) and of even questionable calcinosis (20%), and the absence of steatorrhea. In a series of patients with pancreatic disease reported by Dornberger, Comfort, Wollaeger and Power⁸ there were 12 with a "presumptive" diagnosis of chronic pancreatitis. In approximately one-half of these patients the response to the secretin test was below the lower limit of normal calculated according to the same statistical formula used by us. It is in just such "doubtful" cases that a reliable pancreatic function test is needed most. It is of interest that in the course of our study the diagnosis of several patients who showed a positive response to the starch tolerance test was changed from "suspected" to "certain" on the basis of new developments consisting of progression of the disease, response to pancreatin therapy, or operative findings.

In this study, the starch tolerance test indicated the greatest impairment of pancreatic function in five patients with carcinoma of the pancreas. This is probably explained by the diffuse and widespread nature of the tumor in our cases, which, in addition to causing local destruction of tissue, resulted in occlusion of most of the larger pancreatic ducts. If the tumor growth had been limited to the tail of the pancreas, a negative outcome of the test could have been expected, as reported by Dreiling⁹ in his work with the secretin test. The reason for this is the great reserve capacity of the pancreas, which has been demonstrated by surgical removal of large portions of the pancreas with little or no impairment of digestion.

The results of the starch tolerance test in two other types of partial destruction of the pancreas are of interest. In four patients with penetration of a duodenal ulcer into the pancreas, the test was positive in three cases and "borderline" in one. This unexpected observation indicates either that the involvement of the pancreas in such cases extends far beyond the immediate vicinity of the crater, or that the inflammatory mass around the ulcer has obstructed some major tributaries of the duct of Wirsung, or both. The widespread nature of the injury in three of these four cases was also demonstrated by definite reduction of glucose tolerance.

On the other hand, the results of starch tolerance tests were normal in two patients who had undergone partial resection of the pancreas. In the first of these patients the operation was performed for carcinoma of the second portion of the duodenum; the remaining part of the pancreas, while small, was normal. In the second patient the indication for operation was a cyst of the head of the pancreas, with chronic pancreatitis and intractable pain. A subtotal pancreatectomy was done, leaving a small remnant of normal-appearing pancreatic tissue behind. The normal outcome of the

starch tolerance test in these two cases probably can be attributed to the great reserve capacity of the pancreas mentioned previously.

In a single patient with acute pancreatitis, "borderline" results were obtained in a starch tolerance test performed two weeks after the onset of the attack. Dreiling,¹⁰ working with the secretin test, found that negative results with such a test are of little significance in establishing a diagnosis of acute pancreatitis, probably because by the time the condition of the patient permits the performance of the test the function of the pancreas has returned to normal. On the contrary, a positive outcome of the test in such patients some time after an attack is of considerable value and indicates the beginning of chronic pancreatitis. The same interpretation is probably applicable also to the starch tolerance test.

The mean rise of the blood amino acid nitrogen during the gelatin tolerance test was found to reflect the degree of impairment of pancreatic function in our various groups of patients classified according to clinical criteria, and to show an over-all agreement with the mean results of the starch tolerance test (figure 2 A and B). On the other hand, the results of the individual gelatin tolerance tests showed a great deal of overlapping between the normal and the two abnormal groups. This was reflected in the statistical analysis of the obtained data, which indicated that the test in all patients of both abnormal groups was within the normal limits. For these reasons we consider the gelatin tolerance test in the form used by us unreliable as a pancreatic function test in adults.

There are three possible reasons for failure of the gelatin tolerance test in our experience with adult patients suffering from diseases of the pancreas, as contrasted to its successful use in children with fibrocystic disease of the pancreas. First, the test dose of gelatin used by us was smaller, averaging about 0.7 gm. per kilogram, than the dose of approximately 1.5 gm. per kilogram used in the mentioned studies in children. Against this possibility is the observation by West et al. that larger and smaller doses did not result in important differences in the blood amino acid nitrogen curves. Furthermore, these authors reported a rise of 2.8 to 4.8 mg.% in the amino acid nitrogen level in the blood of their control subjects. The corresponding rise in our controls, ranging from 2.9 to 8.0 mg.%, compares favorably with their figures.

Second, trypsin may conceivably be more important for the digestion of protein in children than in adults, although we are not acquainted with any evidence to support this possibility. Third, in general, fibrocystic disease of the pancreas in children produces an extreme deficiency of trypsin that is equaled only in the most severe cases of pancreatic insufficiency in adults. This is shown by the observation that in children with fibrocystic disease of the pancreas practically no trypsin activity can be demonstrated in the pancreatic juice aspirated from the duodenum.¹¹ The last appears to be the most reasonable explanation of the reported successful use of the gelatin tolerance test in the diagnosis of this disease in children.

SUMMARY AND CONCLUSIONS

1. A new test of pancreatic function based on the amylolytic activity of pancreatic juice in the intestine is described.
2. There was no overlapping of the results of the starch tolerance test performed in 27 individuals without pancreatic disease and in 23 patients with chronic pancreatic disease. In 87% of cases in the latter group the outcome of the test was definitely abnormal (above the mean of the controls plus three times the standard deviation).
3. Among 10 patients with suspected chronic pancreatitis the starch tolerance test was definitely abnormal in 60% of cases.
4. The described test is suitable for use under conditions of ordinary hospital and office practice.
5. A similar test based on the proteolytic activity of pancreatic juice in the intestine, which was also studied, failed to yield results helpful in the diagnosis of pancreatic disease.

ACKNOWLEDGMENT

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HYPERSENSITIVITY AND RHEUMATIC FEVER *

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PART I

HYPERSENSITIVITY

1. Basic concepts of hypersensitivity.
2. Recent studies on antigen.
 - a. The kinetics of antigen in the body.
 - b. Histologic localization of antigen with fluorescent antibody.
 - c. The subcellular localization of antigen.
3. Studies on antibody.
 - a. The sites of antibody formation.
 - b. The rôle of the plasma cell in antibody formation.
4. Experimental hypersensitivity.
 - a. Quantitative studies of the antigen-antibody reaction.
 - b. The abnormal physiology of an in vivo antigen-antibody reaction.
 - c. Immunophysiology.
 - d. Pathogenesis of the histologic lesions in sensitized animals.
 - e. The rôle of the adrenal gland.
5. The Arthus and the Shwartzman phenomena.
6. Autoantibodies.

INTRODUCTION *

It has been postulated that the clinical syndrome which is recognized as rheumatic fever is due to an altered reactivity of the host—a hypersensitivity reaction—to an antigenic substance or substances. The hypothesis was originally based on the numerous histopathologic similarities observed between experimental serum sickness and clinical rheumatic fever.² Subsequent studies have shown that infection with the beta hemolytic streptococcus precedes the development of acute rheumatic fever.

The purpose of the present review is to delineate the extent of our present knowledge of immunology as it relates to the problem of rheumatic fever, and to discuss the evidences available to substantiate the view that acute rheumatic fever is a hypersensitivity phenomenon.

PART I

BASIC CONCEPTS OF HYPERSENSITIVITY

THE phenomenon of hypersensitivity was recognized by the Greeks and Romans, who described it under the term "*idiosynkrasie*." Its systematic study, however, was not begun until about 1905, when von Pirquet and Schick¹ first examined in detail the symptoms and signs of a disease that

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followed the parenteral injection of a foreign protein into human subjects. This disease is now recognized as serum sickness. These investigators explained its manifestations as follows: The foreign protein acted as an *antigen*. The presence of antigen in the body led to the development of *antibody*. Union of antigen and antibody in the organism produced the symptoms and signs of serum sickness. Serum sickness, therefore, was a manifestation of an *in vivo* antigen-antibody reaction. It was postulated that the reactivity of the tissues of the host had been altered. These brilliant hypotheses were based solely on clinical observations, but subsequent experimental studies have proved them to be valid.

As late as 1926, antigens and antibodies were recognized only by their biologic properties. It was not even certain that antibodies existed as material objects. Subsequent investigations have delineated the chemical nature and properties of the antigenic substances and of antibody. No attempt will be made here to review these aspects of the subjects, since they are adequately treated in standard textbooks.^{3,4} It should be mentioned that there is some evidence to suggest that the antigenicity of protein molecules may be related to certain chemical configurations. Williams⁵ found that a reduction in the sulfhydryl content of bovine serum albumin was accompanied by a simultaneous reduction in antigenicity; he suggested that the antigenic power of this protein may be largely dependent on the presence of reactive sulfhydryl groups.

RECENT STUDIES ON ANTIGEN

The Kinetics of Antigen in the Body: Prior to the introduction of radioactive isotopes, no satisfactory simple method was available for studying the distribution and localization of antigen in animals, although the blue azoprotein dyes were previously employed as tracer antigens.⁶ Antigens may now be labeled with artificially produced radioactive isotopes such as iodine¹³¹, phosphorus³² and sulfur³⁵. By tracing the radioactivity it is possible to determine the distribution and persistence of the antigen in the tissues and even in subcellular units.

One of the earliest studies employing this technic was that of Libby and Madison,⁷ in which a complex antigenic substance, tobacco mosaic virus, was labeled in the nucleoprotein fraction with P³². When the purified virus was injected into mice, most of the radioactivity was observed in the liver. Circulating antibody was detected as early as 48 hours after injection of the tagged virus. The biologic "half-life" value (the time required for a 50 per cent drop in concentration) of the virus was about two days; that of the circulating antibody was between six and seven days. The time when probable complete breakdown of the virus occurred coincided with the initiation of a linear increase in the amount of circulating antibody; this fact was interpreted as indicating that antigen must be present to stimulate the formation of antibody.

In most subsequent studies with tagged antigens, purified antigenic substances have been used. Traceable amounts of I^{131} can be added to almost any protein without altering the protein immunologically. Protein antigens tagged with I^{131} appear to retain the radioactive label in vivo and in vitro, as long as they are immunologically active.⁸ Therefore, the localization of the radioactivity serves as a valid method for determining the distribution of the antigen. Radioautography makes possible the approximate histologic localization of the labeled antigen.

Dixon, Bukantz, Dammin and Talmage⁹ found that when homologous rabbit globulin labeled with I^{131} was injected intravenously into rabbits, equilibration of the globulin between the intravascular and extravascular components of the plasma protein pool took place, the extravascular fluid containing twice as much globulin as the vascular fluid. The half-life of homologous globulin in rabbits is about two days. When bovine gamma globulin labeled with I^{131} was injected intravenously into rabbits, its concentration in the blood paralleled that of labeled homologous globulin for the first four days, indicating that the body's utilization of heterologous and homologous globulin is similar. After the fourth day, however, the rate of disappearance of the bovine gamma globulin from the blood was sharply increased. This rapid disappearance was thought to be due to the development of antibody. The elimination of this tagged bovine globulin from the various tissues paralleled approximately its elimination from the blood.

Detectable circulating antibody appeared on the seventh day after injection, at which time virtually all the antigen had disappeared. Hence, although the first antibody was produced in the presence of antigen, the major part of the antibody production took place in the absence of extracellular antigen. Further studies in animals treated with roentgen-rays and in previously sensitized rabbits confirmed this relationship between the development of antibody and the rapid disappearance of antigen from the extracellular fluid. Indeed, the antigen disappearance rate has been suggested as an index of the immune response.

Histologic Localization of Antigen with Fluorescent Antibody: The localization of various antigenic substances by histologic methods has been made possible through the use of fluorescent antibodies. Coons¹⁰ has evolved a method for conjugating purified antiserum with fluorescein isocyanate and of employing this material as a histochemical tool. After antigen is injected into animals, they are killed and tissue sections are made. The sections are then treated with the fluorescein-tagged specific antiserum. The antibody is precipitated in those areas of the tissues containing antigen. The excess nonprecipitated antibody is then removed by appropriate washing of the sections. The antibody can be identified by its bright blue fluorescence in ultraviolet light.

Studies by this technic in mice which were given intravenous injections of foreign substances, such as bacterial polysaccharides or animal proteins, showed that these substances rapidly left the blood stream and appeared in

the connective tissue of all the organs examined. They were also found in high concentrations in the phagocytic cells of the reticuloendothelial system. There were striking differences in the rates of disappearance of various antigenic substances from the blood stream. Crystalline egg albumin, for example, disappeared within a few hours, whereas human gamma globulin persisted for a week. The rate of disappearance of the protein antigens appeared to be inversely proportional to the molecular size of the antigen. In contrast to the protein antigens, the capsular polysaccharides of the pneumococci and of Friedländer's bacillus persisted for weeks to months. Of extreme significance was the finding that the protein antigens or fragments thereof regularly appeared in the nuclei as well as in the cytoplasm of all the cells into which they penetrated.

The Subcellular Localization of Antigen: The foregoing experiments demonstrating the intracellular localization of antigen were confirmed by the studies of Crampton and Haurowitz,¹¹ who used differential ultracentrifugation as a tool. When liver homogenates were obtained from animals which had received intravenous injections of proteins labeled with I^{131} , radioactivity was found in the nuclear fractions. Subsequent studies¹² showed that the injected antigen was rapidly incorporated into the small granules (microsomes), and that shortly thereafter it appeared in the larger granules (mitochondria), where it remained for long periods of time. The presence of intravenously injected antigen in cellular granules indicates that antigen passes rapidly through the membranes of the liver cells. Since the molecule of ovalbumin, which was used in this particular study, is a macromolecule which is not able to cross semipermeable membranes passively, it must be assumed that the incorporation occurred by some process similar to phagocytosis. The persistence of antigen in the mitochondria is of particular interest, because the large granules have been considered as self-producing units—that is, as sites of protein synthesis.¹³ The present experiment indicates that they may also be sites of antibody production, and hence lends support to the hypothesis that antibody synthesis is essentially protein synthesis modified by the presence of antigen.¹⁴

STUDIES ON ANTIBODY

The Sites of Antibody Formation: Many years ago, Hektoen¹⁵ demonstrated that the total-body exposure of experimental animals to ionizing radiation suppressed the usual antibody response to antigens injected shortly before or after the exposure. He ascribed this suppression to the destructive effect of irradiation on lymphatic tissue and bone marrow. These findings have been confirmed by others.¹⁶ Recently Jacobson, Robson and Marks¹⁷ have demonstrated that if the spleen or appendix of the rabbit is protected by a lead shield during total-body irradiation, the capacity to produce antibodies is retained to a marked degree, even though lymphatic tissue elsewhere in the body is temporarily destroyed.

A clearer delineation of the sites of antibody formation now appears to be in prospect. Ranney and London¹⁸ have developed a technic for determining the capacity of various tissues to synthesize antibodies *in vitro*. Immunized animals are killed at a time when the antibody titer of their serum is high, and presumably when antibody is being actively synthesized. It is possible to obtain from the bodies of these animals tissues which are capable of forming antibody. When such tissue is incubated with an isotopically labeled amino acid, it utilizes the acid for the synthesis of new antibody protein. Specific antigen is then used to precipitate antibody from the tissue. If this antibody is radioactive, the capacity of the tissue for forming antibody has been proved. By the use of such a method in rabbits, following the injection of killed pneumococci, it has been shown that the spleen and liver are capable of synthesizing antibody *in vitro*; so far, however, such synthesis has not been demonstrated in kidney tissue.

The Role of the Plasma Cell in Antibody Formation: The exact cell type responsible for the production of antibody has long been a matter of controversy. European investigators have suspected for some time that the plasma cell is the important one. Bjornboe and Gormsen,¹⁹ for instance, found that the hyperimmunization of rabbits caused marked proliferation of plasma cells in the spleen and other organs. On the other hand, Harris and Harris²⁰ have suggested that the lymphoid cells are the ones primarily concerned in antibody production.

The synthesis of protein is apparently related to the metabolism of nucleic acids. The multiplication of intranuclear chromosomes appears to be associated with the formation of desoxyribose nucleic acid (DNA), whereas the production of cytoplasmic protein is linked with that of ribose nucleic acid (RNA). The production *in vivo* of certain specialized proteins, at least, is related to RNA.

Since the relationship of nucleic acids to the synthesis of proteins appeared to be pertinent to the problem of antibody production, Ehrich, Drabkin and Forman²¹ compared the formation of antibody (one type of protein) in rabbit lymph nodes draining areas injected with typhoid vaccine with the changes in the nucleic acid content of the nodes. It was observed that the changes in the total DNA content of the lymph nodes paralleled the changes in the weight of these nodes. This finding is in accord with the view that the production of DNA is associated with the multiplication of chromatin. It was suggested that after the initial exudative phase, the increase in weight of the lymph node following the injection of antigen was due largely to multiplication of cells. The RNA content of the nodes increased most sharply between the fourth and sixth days after the injection of vaccine, when antibody formation was also at its maximum.

Histologic studies of the nodes revealed that, during the first six days after injection, plasma cells were predominant. During the first three days plasmablasts predominated; on the fifth and sixth days mature plasma cells were the prevailing cells. Most of the RNA was contained in the plasma

cells. In contrast, the lymphocytes did not show their greatest activity until the ninth day, when the formation of RNA and antibody had passed its peak.

Coons²² has recently used the previously mentioned fluorescent antibody technic to study antibody response in the rabbit. Frozen sections of tissues containing antibody were dipped in a dilute solution of homologous antigen and carefully washed. The sections were then treated with fluorescein-labeled antibody, and the original antibody was localized by visualization of the fluorescent antibody. By such means, the response to egg albumin, human gamma globulin and diphtheria toxoid was investigated.

Antibody was first detected in the regional lymph nodes four days after the subcutaneous injection of such a soluble protein. At that time it was found in occasional cells scattered singly in the medullary cords and around the periphery of the lymphoid follicles, but only rarely within them. These cells had large nuclei which often contained traces of antibody, and a thin rim of cytoplasm which contained it in high concentrations. At later stages (six to eight days) the number of cells involved was not notably increased, but they had become typical plasma cells. When antigen was injected into previously sensitized animals, antibody was first detected on the second day in cells younger than those described above; their development followed the same course, however, many more cells were involved, and they were grouped in colonies, suggesting that the descendants of some scattered primitive cells were now all engaged in antibody synthesis.

These data confirm the conclusions of Bjornboe and others¹⁹ that the plasma cell is the major source of antibody under the conditions described, although the possibility of smaller contributions by other types of cells is not excluded.

EXPERIMENTAL HYPERSENSITIVITY

Quantitative Studies of the Antigen-Antibody Reaction: Recent application of quantitative methods to the study of anaphylaxis has delineated more precisely the extreme sensitivity of the antigen-antibody reaction. By the use of a single purified antigen, a mathematical expression of the interaction of this substance with its homologous antibody has been made possible. The amount of antibody may be expressed in terms of the nitrogen content of the serum. Of extreme interest is the finding that the severity of certain of the biologic reactions which occur in vivo is related to the amounts of these agents which interact. For instance, Fischel and Kabat²³ found in rabbits that the local intracutaneous injection of 0.025 mg. of anti-egg albumin nitrogen produced minimal Arthus reactions, and that the severity of the reaction increased with the quantity of antibody injected. Once a threshold quantity of antibody was exceeded, the amount of antigen injected had little effect on the reaction. The injection of antigen at several sites in rabbits passively sensitized by intravenous injection of anti-egg albumin gave reactions of reduced intensity.

The Abnormal Physiology of an in Vivo Antigen-Antibody Reaction: Early experimental and clinical observations have established the fact that the union of antigen and antibody in vivo results in an abnormal increase in capillary permeability. In acute anaphylactic reactions, this phenomenon may be so severe as to cause hemoconcentration and peripheral circulatory collapse. It is generally stated that cell damage results in the liberation of histamine and that the physiologic changes which follow can be explained, at least partially, as due to the pharmacologic effects of histamine.²⁴

Copenhaver, Nagler and Goth²⁵ have found that histamine located intracellularly in liver homogenates is concentrated predominantly in the mitochondrial fraction. Whole homogenates contained an average of 46 micrograms of histamine per gram of fresh weight, distributed as follows: nuclei, 15 per cent; mitochondria, 52 per cent; microsomes, 13 per cent; and supernatant, 17 per cent.

Although extensive studies have been made on the histologic changes associated with experimental serum disease, very little information is available concerning the *physiologic* changes. Mikulicich²⁶ found that in unanesthetized rabbits electrocardiographic abnormalities occurred almost invariably during the anaphylactic reaction. These changes were also observed with passive sensitization of rabbits.

Immunophysiology: Although it has been known and accepted that an anaphylactic type of hypersensitivity reaction increases the permeability of the capillary membrane, few studies are available concerning the effect of such a reaction on the permeability of *cell* membrane. If the deleterious antigen-antibody reaction occurs within tissue cells or on their surface, one might expect an abnormal increase in the permeability of such tissue cell membranes.

On the basis of this hypothesis, a series of studies was undertaken to determine the relative volumes of the vascular and the extracellular compartments. In rabbits sensitized with a large intravenous dose of human plasma, the plasma volume and the thiocyanate space were determined at the time humoral antibody was first detected.²⁷ (In the presence of intact cell membranes, the thiocyanate space serves as an index of the functional extracellular fluid volume.) A significant decrease in the plasma volume and increase in the thiocyanate space were found; the increase in the thiocyanate space could not be attributed solely to a rise in the extracellular fluid volume due to retention of fluid, since the body weight did not increase proportionately. These changes were interpreted as being indicative of an increase in the permeability of both capillary and cell membranes. The fact that the physiologic changes occurred at the time humoral antibodies appeared suggests that the alterations may have been directly or indirectly due to an antigen-antibody reaction. Subsequently, rabbits sensitized with human serum albumin or globulin showed similar changes.²⁸ An increase in the thiocyanate space was also noted during quantitative passive transfer experiments in rabbits.²⁹

Another group of rabbits sensitized with human plasma developed humoral antibody after a mean interval of 6.5 days. In this group no changes were noted in the blood volume or thiocyanate space. Tissue analyses revealed that the radiosodium space of the adrenal gland was significantly increased in those animals given injections of untreated plasma, but not in animals given denatured plasma or no antigen at all. No such increase was noted in 14 other tissues and organs studied. The water content of the tissues and organs studied did not show any significant variations.³⁰

In other studies rabbits received repeated subcutaneous injections of horse serum over a period of seven months. It was found that a striking increase in the radiosodium space, without an associated increase in body weight, resulted from the injections of antigen which followed the initial sensitization procedure.³¹ This change occurred within 24 hours after an injection of the antigen and persisted over a week. Such an increase is difficult to explain solely on the basis of shift of body water, and it was therefore interpreted as being due to an increase in the permeability of tissue cell membrane to the radiosodium ion.

Pathogenesis of the Histologic Lesions in Sensitized Animals: Since Rich and Gregory³² reported the experimental production of periarthritis nodosa and histologic lesions resembling those of rheumatic carditis and pneumonitis by the sensitization of rabbits with massive doses of horse serum, numerous further experimental studies of this type have been carried out. Although lesions of the myocardium and heart valves have been produced by the injection of various foreign proteins, and although all investigators have recognized that these lesions are similar to those of acute rheumatic fever, they have seldom been regarded as identical. The fact remains that all attempts to produce in experimental animals the prototype of rheumatic fever as it affects human beings have been unsuccessful. The highest incidence of experimentally produced lesions of the valve and valve ring has been reported by More, Waugh and Kobernick, who injected massive intravenous doses of bovine gamma globulin into rabbits.³³ These lesions, however, were not regarded as being identical with those of human rheumatic fever.³⁴ Equine gamma globulin produced little reaction.³⁵ It is of interest also that rabbits given repeated massive injections of horse serum did not reveal significant histologic lesions.³⁶

The cardiac lesions of serum disease can be prevented by desensitization of the animals or by the administration of antihistamine drugs,^{37, 38} as well as by giving cortisone or salicylates in sufficient dosages to sensitized animals.^{39, 40} Nitrogen mustard suppresses both antibody formation and the development of vascular lesions in rabbits given a massive intravenous injection of horse serum.⁴¹ Roentgen radiation inhibited the formation of precipitins for whole bovine serum and bovine serum gamma globulin in the rabbit; in animals so treated, histologic lesions did not develop. The development of characteristic lesions has been correlated with a sudden fall

in complement titer, which does not occur when antibody formation is inhibited. This observation suggests that serum complement may play a significant rôle in the pathogenesis of anaphylactic tissue lesions.

Of greatest significance in such pathogenetic studies have been the recent experiments of Murphy and Swift,⁴² in which group A streptococci were used to give repeated intracutaneous infections to rabbits. Successive infections were produced by a serologic type heterologous to those previously employed. Cardiac lesions closely resembling those found in rheumatic fever were observed in the rabbits that sickened following such a procedure. In addition, the adrenal glands of rabbits which died or were killed while sick, following several intracutaneous streptococcal infections, showed a striking increase in size. Microscopically, hyperplasia, hypertrophy and necrosis of fascicular zone cells were seen. There was a striking correlation between the degree of macroscopic enlargement of the fascicular zone of the adrenal cortex and the occurrence of myocardial granulomas. It seemed probable that the relatively long experimental period and the reconditioning that the animals' tissues underwent as a result of several focal infections with different types of group A streptococci were important factors in the pathogenesis of these lesions. The over-all histopathologic picture in rabbits repeatedly infected with streptococci bore a closer resemblance to that of human rheumatic carditis than did carditis produced by experimental serum disease.⁴³

Robinson has also reported that in rabbits subjected to streptococcal injury the degree of adrenal hyperplasia was related to the severity of the carditis. This hyperplasia was found again largely in the zona fasciculata of the adrenal cortex.⁴⁴

The Rôle of the Adrenal Gland: The striking clinical response shown by some patients with acute rheumatic fever to the administration of cortisone or ACTH has rekindled interest in the rôle played by the adrenal gland in the pathogenesis of this syndrome. Recent studies suggest a relationship between the phenomenon of hypersensitivity and the hyperadrenal state.⁴⁵ In rabbits immunized with pneumococci and given cortisone from the onset of immunization, the concentration of circulating antibody at the ninth and fourteenth days was lower than in control animals which were sensitized but not given cortisone. Germuth and Ottinger⁴⁶ confirmed these observations. This decrease in antibody concentration could be attributed to augmented catabolism of the protein, to a lack of synthesis of antibody globulin, or to both factors.

To investigate this point further, Fischel, Stoerk and Bjornboe⁴⁷ studied the disappearance of passively administered antibody globulin in normal and cortisone-treated animals. No difference was found in the rate of disappearance in the two groups. It was therefore concluded that cortisone did not increase the breakdown of antibody globulin. Marshall and Friedberg⁴⁸ showed that cortisone inhibited the incorporation of a C¹⁴-labeled amino acid, such as glycine, into protein. It was suggested that the low antibody

levels obtained in the active immunization experiment may be ascribed to an interference with the synthesis of globulin by cortisone. In agreement with these experimental studies is the observation of Stollerman, Rubin and Plotz⁴⁰ that the Prausnitz-Küstner reaction produced when antibody is passively administered to human subjects is not altered by cortisone. However, the clinical efficacy of cortisone in allergies is thought to have little relationship to antibody inhibition.⁴⁵

The results obtained in the studies on the effects of ACTH and cortisone on acute anaphylaxis are variable. These studies are, however, subject to the criticism that it is difficult to expect a pharmaceutical agent to prevent the effect of an extremely potent stimulus. Although different species of animals have shown differences in response, cortisone and ACTH appear to afford no appreciable protection against anaphylactic shock in the guinea pig.⁶⁰ ACTH has no effect on the Arthus reaction, which is passively induced with known amounts of antiovalbumin nitrogen and crystalline egg albumin. It appears, therefore, that once antibody is present the reaction between antigen and antibody is not altered by the administration of ACTH or cortisone.

It is customary to differentiate between the anaphylactic type of hypersensitivity reaction and the so-called bacterial allergy or tuberculin type of reaction. In the latter, a pure tissue reaction is thought to occur. The tuberculin reaction in guinea pigs has been completely suppressed by the use of very large quantities of cortisone.⁶¹ A moderate dose does not appreciably inhibit this reaction. In human subjects, smaller doses of hormones do not alter the tuberculin reaction; yet such doses are sufficient to control the manifestations of an underlying disease such as rheumatoid arthritis or rheumatic fever.

It is known that cortisone inhibits the formation of granulation tissue and fibroblasts *in vivo*.⁶² It has been shown that the suppression of allergic encephalomyelitis⁶³ in the guinea pig by the administration of cortisone is due to a lack of reaction around the site of injection of the antigenic substance. The problem of tissue reactivity and its hormonal regulation requires further clarification.

Seifter, Ehrlich, Begany and Warren⁶⁴ reported that cortisone lessened the arterial and cardiac manifestations of serum disease in the rabbit. A marked decrease in adrenal weight, due to atrophy of the zona fasciculata, was noted. Hyaluronidase increased the arteritis and carditis. This finding suggests that cortisone may have caused a generalized suppression of the permeability of the ground substance. That cortisone may have an antipermeability effect had been previously reported.^{65, 66}

That ACTH may exert an inhibitory effect on the development of the cardiovascular lesions of hypersensitivity has been reported.⁶⁷ Germuth, Nedzel, Ottinger and Oyama⁶⁸ have studied the anatomic changes produced by compound E and ACTH in rabbits sensitized with crystalline egg albumin. The adrenals of the animals given compound E were found to

weigh on the average only one-half as much as the adrenals of the controls, but approximately the same as those from normal rabbits. Histologically, the fascicular zones of the cortices appeared to be narrower in the animals given compound E. In contrast to the small adrenals of these animals, the adrenals of the animals given ACTH were large; they were, however, lacking in lipid. Treatment with either ACTH or compound E produced atrophy of the lymphoid tissues, including the thymus and spleen, and a lymphocytopenia. It has been suggested that the reductions noted in serum antibody levels following treatment with hormones might have resulted from these marked changes in the lymphoid tissue.⁶⁰

The Arthus and the Schwartzman Phenomena: The manner in which hypersensitivity reactions produce tissue damage is obscure. Thomas and Stetson⁶⁰ and Stetson⁶¹ have recently reported a series of studies in animals in which the Schwartzman and Arthus phenomena have been used as laboratory models. The Schwartzman phenomenon was produced by the intradermal injection of bacteria or bacterial endotoxin as the preparatory factor. The subsequent intravenous injection of the same bacterial product resulted in a profound tissue alteration at the site of the preparatory injection, which was characterized by the appearance of petechiae and hemorrhagic necrosis. The fundamental lesion appeared to be of vascular origin, consisting of occlusion of the capillaries and small veins by masses of leukocytes and platelets—platelet thrombosis—and followed by hemorrhage and necrosis.

A lesion indistinguishable grossly and microscopically from this was also observed in the experimental Arthus phenomenon, a reaction which has been thought to be based on an *in vivo* antigen-antibody response. Such lesions were also observed in all cases studied at autopsy which showed evidence of active rheumatic carditis, and in none of the other cases. It is not known whether these cellular thrombi are related to the development of any of the other histopathologic changes characteristic of rheumatic carditis.

Autoantibodies: Autoantibodies or anti-tissue antibodies have been suggested previously as being responsible for a variety of diseases. Cavelti⁶² claimed that antibodies against heart tissues exist and can be detected by the collodion particle technic. Subsequent investigators, however, have been unable to confirm his findings.⁶³ Pressman^{64, 65} has recently reported a series of investigations in which anti-kidney and anti-lung antibodies labeled with radioactive iodine or sulfur were injected into rabbits and localized by following the radioactivity. The antisera were prepared by injecting rat lung or kidney tissues into rabbits. It was found that antibodies present in antisera prepared against kidney tissue were concentrated chiefly in the kidney, although there was also some localization in the liver; antibodies in sera prepared against lung tissue were found to localize primarily in the lung and kidney. The half-life of the antibody localizing in the kidney was approximately 20 days, indicating that it cannot be metabolized by the cells. The radioantibody was localized primarily in the glomeru-

lar tuft within a single passage through the kidney. Although of extreme theoretic interest, this technic has not to date demonstrated the existence of a specific antibody against cardiac tissue.

PART II

RHEUMATIC FEVER

1. The rôle of the streptococcus in its pathogenesis.
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PART II

RHEUMATIC FEVER

THE RÔLE OF THE STREPTOCOCCUS IN ITS PATHOGENESIS

Epidemiologic Evidences: Almost everyone interested in the pathogenesis of rheumatic fever now agrees that group A beta hemolytic streptococcal infections play an important rôle in the etiology of this disease. The evolution of this concept dates back many years. As early as 1886, Haig-Brown⁶⁶ reported that rheumatic fever behaved as an epidemic disease and that it was associated with epidemics of pharyngitis or tonsillitis. Following attacks of tonsillitis in 345 previously healthy boys, the subsequent appearance of heart disease was noted in 29 of them (an incidence of 8.4 per cent) after an incubation period.

During World War I numerous epidemics of rheumatic fever, with evidences of bed-to-bed infection, were reported. In 1931, Coburn⁶⁷ correlated the incidence of rheumatic fever with that of hemolytic streptococcal infections, and insisted that every attack of rheumatic fever must be preceded by such an infection. He described three distinct clinical phases in the evolution of the rheumatic attack: (1) acute respiratory infection (usually lasting not more than three days); (2) afebrile asymptomatic period (14 days), and (3) phase of acute rheumatism (one or more cycles lasting 10 to 14 days and separated by periods of remission lasting seven to 10 days). The streptococcal infection was not considered to be the direct cause of the disease, but was thought to act only by initiating some more complex mechanism in the host.

Coburn felt that phase two was crucial in the genesis of the rheumatic activity. The only abnormality found in this symptom-free period was a diminution of serum complement.

The following evidences, collected during the past 20 years, suggest that

the hemolytic streptococcus is in some way related to the development of the rheumatic state:

1. Rheumatic fever has been found to follow known hemolytic streptococcal infections, particularly of the respiratory tract.⁶⁷

2. Epidemics of rheumatic fever are known to follow outbreaks of scarlet fever or streptococcal sore throat.⁶⁸

3. Recrudescences of activity frequently appear when infections by beta hemolytic streptococci occur in persons who have previously undergone attacks of rheumatic fever.

4. High titers of various anti-streptococcus antibodies and cutaneous hypersensitivity to products or fractions of the streptococcus are usually demonstrable in persons suffering from acute rheumatic fever, or from recurrences of this disease.

During World War II it became possible in the armed forces to perform detailed studies of large groups of individuals in whom beta hemolytic streptococcal infection of the respiratory tract had occurred; this approach is rarely feasible in civilian populations. Although rheumatic fever had previously been considered a disease of childhood, these observations indicated that young adults are also susceptible.

Rantz, Boisvert and Spink⁶⁹ found that rheumatic fever is but one syndrome and a small part of the whole complex involved in the so-called post-streptococcal state. In this particular study, all patients with respiratory infections were admitted to a station hospital. Approximately 1,500 patients were observed. Of these, 1,100 with upper respiratory infections did not have streptococci by culture; rheumatic fever did not develop in any of these cases. Those with streptococci in the throat were transferred to a special ward; there were 410 in this group. Clinical rheumatic fever appeared in 14 of these patients, an incidence of 3.7 per cent. It was found, in addition, that some patients who did not feel entirely well after an infection with beta hemolytic streptococci showed laboratory evidences of smoldering rheumatic activity. In the cases studied, there was no phase two or latent period as described by Coburn⁶⁷; instead, there was evidence of continued activity of the disease process for 14 to 40 days during the so-called latent period before the onset of the rheumatic symptoms.

The extensive epidemiologic studies being conducted in a military population at the Francis E. Warren Air Force Base in Wyoming by the Streptococcal Disease Laboratory of the Armed Forces Epidemiologic Board confirm the results of the earlier studies.⁶⁹ Over a period of three years the attack rate for rheumatic fever among individuals known to have had streptococcal infections was relatively constant (2.4 to 3.1 per cent) throughout the period of study, and was independent of the season. The data failed to show that the child is more susceptible to rheumatic fever than the adult, but suggested that the higher incidence of rheumatic fever in the young age group is related to a higher incidence of streptococcal infections.

There was little evidence that the severity of the disease produced by the group A streptococcus altered the attack rate for acute rheumatic fever. The attack rate bore no significant relation to the type of streptococcus isolated. It was found that a previous attack of rheumatic fever increased the risk of recurrent attacks following a streptococcal infection. A positive correlation was established between the magnitude of the antibody response (antistreptolysin) and the attack rate of acute rheumatic fever. The data suggest that persons who develop rheumatic fever respond in an altered fashion immunologically.

Immunologic Evidences: The early confusion regarding the classification of beta hemolytic streptococci was resolved by the studies of Lancefield⁷⁰ and Griffith.⁷¹ At the present time, 12 groups of beta hemolytic streptococci are recognized; this serologic grouping is made possible by the identification of a group-specific carbohydrate substance, C, which is a somatic antigen and forms a precipitate in the presence of its group-specific antibody.

Most human infections are caused by group A beta hemolytic streptococci. This group of organisms has been subdivided into more than 40 different types, on the basis of a serologic reaction to another somatic antigenic fraction, the M protein. Immunity against infection is dependent on immunity against the type-specific M substance. For instance, a person recovering from an infection with type 1 streptococcus will be immune to reinfection by type 1, but he will not necessarily be immune to infections by other types. In the study reported by Rantz, Boisvert and Spink,⁶⁸ it was found that recrudescences of the rheumatic process could be incited by reinfection of the patients with new types of streptococci. Furthermore, the duration of this type-specific immunity is variable and probably lasts only a few months. A comprehensive discussion of this problem of the antigenic components of the group A streptococcus has been given by Swift.⁷²

The antigens most frequently studied in an effort to determine the relationship of the streptococcus to rheumatic fever have been the extracellular products of the streptococcus. Among these are streptolysin O, fibrinolysin, hyaluronidase and the erythrogenic toxin. Todd⁷³ was the first to establish a clear relationship between streptococcal infections and the streptolysin antigen. He showed that in the serum of animals a reaction to streptococcal infection can be detected and measured by the presence of antibody against the streptolysin. He suggested that the presence of anti-streptolysin in the serum of patients with rheumatic fever was evidence that this disease was preceded by a hemolytic streptococcal infection. Longcope,⁷⁴ however, found no correlation between the severity of the rheumatic process and the height of the antistreptolysin titer. Taran, Jablon and Weyr⁷⁵ concluded that the presence of a high antistreptolysin titer in the serum of a rheumatic patient did not necessarily denote rheumatic activity.

Mote and Jones⁷⁶ found that, in a high percentage of patients convalescent from hemolytic streptococcal infections, antibodies develop to one or more of the hemolytic streptococcal products. The data failed to reveal

that scarlet fever and the usual streptococcal pharyngitis showed any basic difference in their capacity to produce in the host an antibody response to one of the substances tested at some time during convalescence. The presence of nonsuppurative complications, however, tended to increase the probability of an antibody response.

There was found to be an association between attacks of rheumatic fever, whether primary or recurrent, and the presence of hemolytic streptococcal infections. Seventy-seven per cent of severe recurrences were associated with clinical evidences of respiratory tract infection. Even in the absence of clinical symptoms of infection, serologic tests showed that severe recurrences of rheumatic fever in patients with inactive rheumatism were usually preceded by a hemolytic streptococcal infection, or associated with such an infection. On the other hand, symptomatic respiratory infections, including sore throat, could occur during the inactive phase and produce serologic evidence of hemolytic streptococcal infection without reactivating the rheumatic process. There appeared to be no basic difference qualitatively between the antibody response of the rheumatic and the nonrheumatic individual to the hemolytic streptococcal products.

On the other hand, recent studies at the Warren Air Force Base⁶⁹ have indicated that, in general, individuals with acute rheumatic fever have higher concentrations of antibody in the serum than those who have streptococcal infections without rheumatic fever. Quinn and Liao⁷⁷ found that the titers of the antienzymes (antihyaluronidase, antistreptolysin "O" and antistreptokinase) of the patients who acquired rheumatic fever following a hemolytic streptococcal infection were significantly higher than those in patients with uncomplicated hemolytic streptococcal infections. Furthermore, the antibody titer remained high for a longer period of time, and the return to lower levels required a much longer time in patients with rheumatic fever than in those who recovered without complications. Similar observations have been reported by Windblad⁷⁸ and by Rothbard, Watson, Swift and Wilson.⁷⁹

Evidences from Prophylactic Studies: It is apparent that if rheumatic fever is usually, if not always, preceded by a streptococcal infection, prevention of such infections should do much to lower the incidence of the disease. Soon after sulfanilamide was introduced, it was found to have a favorable effect on the course of streptococcal infections in man and in experimental animals.⁸⁰ It was thought that sulfanilamide might afford protection against recurrent attacks of rheumatic fever by preventing the preceding streptococcal infection. The use of such prophylaxis in rheumatic patients effected an 86 per cent reduction in the number of recurrent attacks of acute rheumatic fever.⁸¹

During the last war extensive studies were conducted to determine the value and limitations of sulfonamides as prophylactic agents in rheumatic fever. Although sulfadiazine was found to decrease the incidence of streptococcal infections while it was being administered, the attack rate returned

to control levels shortly after the drug was withdrawn.⁸² It became apparent that, since sulfadiazine is a bacteriostatic compound and streptococci are not eradicated from the population receiving the drug, it would have to be given almost continually. The extensive studies in the Navy by Coburn and Young⁸³ demonstrated that the streptococcus may become resistant to sulfonamide drugs.

Penicillin, a bactericidal agent, was next introduced. Preliminary reports indicate that penicillin may prevent streptococcal infections and rheumatic fever, but the optimal method of administration has not been determined.^{84,85} Although the chemoprophylaxis of streptococcal respiratory infections may not be practical as a means of preventing initial attacks of rheumatic fever in the general population, the results of such studies offer additional circumstantial evidence of the relationship between rheumatic fever and a preceding streptococcal infection.

The incidence of rheumatic fever is lowered by *treatment* of streptococcal respiratory infections as well as by their prevention. In a carefully controlled study of a military population, Rammelkamp and his co-workers⁸⁶ found that the treatment of streptococcal upper respiratory infections with procaine penicillin reduced the attack rate of rheumatic fever by 96 per cent. Of 798 patients whose streptococcal disease was treated with penicillin, only two acquired definite acute rheumatic fever, whereas in a control group of 804 untreated subjects the disease developed in 17.⁸⁷ Early and effective penicillin therapy suppressed antistreptolysin O response and eradicated the streptococci in many cases.⁸⁸ Antibody response to streptokinase was also suppressed by such a measure.⁸⁹ Therapy with Aureomycin and Terramycin, as well as penicillin, has inhibited antibody formation (antistreptolysin O production)⁹⁰ and reduced the incidence of rheumatic fever.⁸⁸

THE HOST FACTOR

Wilson and Schweitzer⁹¹ noted the familial incidence of rheumatic fever and concluded that it tended to be hereditary. The data best fitted the interpretation that the susceptibility was transmitted as a single autosomal recessive gene, although the presence of such a gene was not thought to be the sole condition essential for the development of rheumatic fever. Thus, the pathogenesis of rheumatic fever was thought to be related to a peculiar reaction of certain individuals to infection with the streptococcus.^{68,74} The specific inherited characteristic was thought to be an immunologic hyper-reactivity.

Several recent studies have been reported which were intended to test the hypothesis that the exaggerated antistreptococcal antibody response in rheumatic patients is part of a generalized hyperreactive immunologic capacity. Perry, Hahn and Rammelkamp⁹² immunized with either cholera vaccine or Vi antigen 579 men with untreated exudative pharyngitis. When the antibody responses to Vi antigen or cholera were compared with those

to streptolysin O, no correlation was observed in men with group A streptococcal pharyngitis who did not have rheumatic sequelae. The 21 men in whom rheumatic fever developed exhibited a significantly higher titer of antistreptolysin O than those who did not have this complication, but no increased response to Vi antigen or cholera vaccine was observed. This study failed to demonstrate the existence of a generalized hyperreactive capacity in individuals susceptible to rheumatic fever.

Miller, Kibrick and Massell⁸³ immunized children in the convalescent stage of rheumatic fever with either polyvalent influenza vaccine or monovalent typhoid vaccine; they found no evidence for the existence of a general hyperreactivity of immune response. Quinn, Seastone and Dickie⁸⁴ showed that individuals with a history of rheumatic fever or with rheumatic heart disease showed no gross or consistent tendency to produce larger amounts of pneumococcus antipolysaccharide and no greater degree of skin sensitivity to tuberculin than did individuals without such a history.

The hypothesis that rheumatic fever is related to some sort of hypersensitivity to beta hemolytic streptococcus is not necessarily invalidated by the results of these studies, however. There is no method available for comparing the relative magnitude of the antigenic stimulus in individuals who do and those who do not develop rheumatic fever following streptococcal infections. The streptococcal infection may be unique in producing this peculiar hypersensitivity, and there is the possibility of the development of a sensitizing nonprecipitating antibody. Genetic variations have been shown in the ability of the mouse to produce demonstrable circulating antibody to either egg albumin or pneumococcus polysaccharide.⁸⁵ It is also known, however, that in the mouse antibodies to antigens of different chemical constitution are not formed in an identical manner. The above studies in human beings suggest that the human organism also reacts differently to dissimilar antigenic stimuli.

The Role of Hypersensitivity: The many histologic and clinical similarities between acute rheumatic fever and serum sickness, both experimental and clinical, have been previously reviewed.² There is no doubt at the present time that serum sickness is a manifestation of an *in vivo* antigen-antibody reaction. The study by Murphy and Swift⁴² suggested that repeated sensitization of rabbits with different types of group A streptococci may produce histologic lesions most closely resembling those of rheumatic fever; the incidence of the lesions was approximately the same as the incidence of rheumatic fever in a population infected with group A streptococci.

The salicylates are the only drugs which have withstood the trial of time in the therapy of acute rheumatic fever. It is of interest that some of the early studies on the pharmacology of salicylates suggested that they might affect the immune response. Swift, in 1922,⁸⁶ found that their administration to sensitized animals resulted in a depression of antibody formation. Several years later⁸⁷ he reported that the distressing symptoms of arthritis in rheumatic fever were readily controlled by the administration

of salicylates. The exudative features of the disease were found to be less prominent when patients were under the full influence of salicylates than when they were not receiving this drug.

Coburn and Moore⁹⁸ reported that the administration of salicylate to rheumatic subjects during respiratory infections with hemolytic streptococcus and for two weeks after such infections prevented the development of the rheumatic attack or suppressed it below the clinical level. Only one of 47 such patients receiving 5 gm. of sodium salicylate a day had a clinical attack of rheumatic fever, whereas 57 of 139 control patients had clinical attacks. Coburn and Kapp⁹⁹ subsequently showed that sodium salicylate inhibits the precipitation of antigen with antibody *in vitro*.

On the basis of the abovementioned experimental evidences, Coburn¹⁰⁰ treated rheumatic subjects with large doses of salicylates. So far as is known, salicylates do not alter the capacity of the bacterial agent to elaborate antigen, or affect it in any way. The hope was that alteration of the abnormal antibody response would decrease the inflammation of vascular tissue and thus prevent disabling heart disease. However, there is still some doubt at present as to whether massive salicylate therapy actually suppresses the inflammatory reaction in rheumatic fever.¹⁰¹

It has been suggested by Kelemen, Majoros, Ivanyi and Kovacs¹⁰² that large doses of salicylates mobilize the adrenal cortisone-compound F system, whereas small doses do not. Cronheim, King and Hyder¹⁰³ confirmed the finding of these workers that the administration of salicylate to normal rats reduces the amount of ascorbic acid contained in the adrenals. This action was augmented by glycine. The data were interpreted as indicating that the salicylates have a specific effect on the adrenal-pituitary system which is distinct from the general, nonspecific stress reaction.

ALTERATIONS IN FLUID DISTRIBUTION

The Effect of Salicylates: Many clinical investigations on rheumatic fever have been concerned with its immunologic aspects, the rôle played by the adrenal gland, and the question of whether salicylates cure rheumatic fever or merely relieve symptoms. It would seem that a reasonable line of approach to the fundamental problem would be to determine as precisely as possible the nature of the physiologic changes which occur in acute rheumatic fever. That cardiac damage occurs is certain, but the other clinical manifestations of the disease suggest that it is a generalized process. It is strange that, in spite of the extensive use of salicylate in the therapy of this disease, very few studies have been concerned with its mode of action. The effect of the drug on the acute manifestations of rheumatic fever is so striking that, if its exact mode of action were discovered, the nature of the disease process in acute rheumatic fever might be inferred.

Reid,¹⁰⁴ in studying the biochemical changes associated with salicylate therapy in rheumatic fever, found that relief of the acute rheumatic mani-

festations was accompanied by a fall in the carbon dioxide combining power of the plasma, a finding which suggested that some alteration in the acid-base balance of the body fluids was associated with the disease. Secondly, the fall in the erythrocyte sedimentation rate was accompanied by diuresis; this phenomenon suggested that changes in the volume of the body fluids were also involved.

Subsequently, Reid, Watson and Sproull¹⁰⁸ observed the changes in the acid-base balance and in the volume of internal body fluids in adults with rheumatic fever while they were being treated with salicylates. Measurements were made of the body weight, urine volume and nitrogen balance; of the urinary sodium, chloride and potassium; of the plasma pH and plasma carbon dioxide content; and of the plasma volume by the T-1824 dye method. The principal pharmacologic actions of the drug were found to be stimulation of protein catabolism (as indicated by the negative nitrogen balances) and aggravation of a respiratory alkalosis coincident with relief of the well known manifestations of acute rheumatic fever.

It was postulated that, as a result of increased protein breakdown, the distribution of water within the body was profoundly altered. The general effect of salicylate was thought to be to reduce the total volume of body fluids, but the fluid loss from cells, interstitial spaces and plasma was not uniform. The first change was thought to be a reduction in cellular fluid associated with a temporary increase in plasma and interstitial fluid volumes. Later both the plasma and interstitial spaces lost fluid, as was indicated by a fall in plasma volume and the development of diuresis. The relief of joint pain and swelling and the fall in the erythrocyte sedimentation rate were attributed to the removal of water from cells and plasma, respectively. This dehydrating effect was thought to follow the reduction in cellular and plasma protein resulting from increased protein catabolism.

The data suggested that the therapeutic action of salicylates differed in no way from the natural mechanism of recovery, since the biochemical changes in acute untreated rheumatic fever were simply exaggerated by the administration of the drug. It was suggested that salicylates merely speeded up and possibly intensified the natural curative process.

Changes in the Permeability of Membranes: The above interpretations were based on indirect measurements of shifts in body fluids. With the introduction of radioactive isotopes, it has become possible to measure directly the volume of body fluid in which the sodium ion is diluted and also to determine the body contents of exchangeable sodium and potassium. By the injection of a known amount of radioactive sodium intravenously and the determination of its concentration in blood serum three hours later, it is possible to calculate the volume of fluid in which the isotope is diluted. In the presence of intact cell membranes, the radiosodium space is thought to represent a functional physiologic unit, although it by no means measures the anatomic extracellular fluid space.

When such measurements were made in two subjects with acute rheu-

matic fever,¹⁰⁶ the initial values were found to be 46.3 and 36.8 per cent of the body weight. Neither subject had clinically demonstrable edema. In other disease states, values higher than 30 per cent of the body weight were invariably associated with clinical edema.¹⁰⁷ These high values during untreated rheumatic fever were interpreted as indicating an abnormal increase in the permeability of the cell membrane. It is not known whether this alteration is localized to any specific tissue or organ, or whether it is generalized. In both instances, the administration of salicylate resulted in a decrease in the radiosodium space, with a parallel decline in the erythrocyte sedimentation rate and without appreciable changes in the body weight. In one instance, the discontinuation of salicylates during the third week of therapy was followed by an increase in both the sedimentation rate and the radiosodium space—changes which subsided when salicylate therapy was resumed. This sequence of events suggested that the salicylate was suppressing certain physiologic alterations, but that it did not cure the disease.

In the previous section have been described the changes in the plasma volume and the thiocyanate space in experimental and clinical serum sickness¹⁰⁸—changes which were thought to be related to the immunologic processes and indicative of alterations in the permeability of cellular and capillary membranes. The changes in the distribution of body fluids and electrolytes in acute rheumatic fever are compatible with the hypothesis that it is a manifestation of an *in vivo* hypersensitivity reaction.

THE RÔLE OF THE PLASMA CELLS

The results of animal experiments on the rôle of the plasma cell in antibody production have been reviewed in the previous section. Good and Campbell¹⁰⁹ found that plasmacytosis of the bone marrow regularly develops in patients with acute rheumatic fever, disappearing when the rheumatic condition becomes quiescent. This alteration of the bone marrow appears to be closely correlated with the production of gamma globulin in this disease. The bone marrow plasmacytosis was explained as a morphologic expression of the reticuloendothelial response to the antigenic stimulation afforded by contact with group A streptococci and their products. Kolouch¹¹⁰ has previously shown that the immunization of rabbits with streptococcal antigens is regularly accompanied by the development of plasmacytosis in the bone marrow and spleen. The development of mature plasmacytes is associated with the liberation of globulin and specific antibodies into the serum.¹¹¹

THE RÔLE OF THE ADRENAL GLAND

In 1949 it was found that the administration of cortisone or ACTH to rheumatic patients usually resulted in a rapid disappearance of fever, tachycardia and polyarthritis; a return to normal of the electrocardiogram and the sedimentation rate, and a decrease in the concentration of serum globulin

and in the titer of antistreptolysin O.^{112, 118} In six of 10 subjects studied by Massell and his co-workers,¹¹⁴ discontinuation of ACTH was followed by recurrences of the manifestations of rheumatic activity. Three of these patients responded promptly to resumption of therapy or an increase in the dosage. The effects of ACTH were considered to be indirect and to depend upon the stimulation of the adrenal cortex, with a consequent increase in the production of 11, 17 oxysteroids.¹¹⁵ Despite the extensive and numerous subsequent investigations with ACTH and cortisone, their exact mechanisms of action remain unknown. At the present time it is not even certain that ACTH or cortisone is superior to salicylate as a therapeutic agent in acute rheumatic fever. Studies are in progress to determine whether cortisone and ACTH will suppress the inflammatory rheumatic process.

Because of the suspected relationship between rheumatic diseases and the hypersensitive state, and between allergic phenomena and the function of the adrenal cortex, the demonstration of the spectacular effects of cortisone on acute rheumatic fever soon led to extensive studies of the effects of this hormone on allergic reactions. It has been established that ACTH and cortisone will inhibit many experimental allergic reactions, including the Arthus phenomenon⁹⁸ and the cardiovascular and renal lesions associated with experimental anaphylactic hypersensitivity. They depress antibody formation¹¹⁶ and protein synthesis,¹¹⁷ and interfere with the general reactivity of mesenchymal tissue to injury; but they appear to have very little effect on the union of antigen and antibody *in vivo*, either in the circulation or in the tissues.¹¹⁸ It has therefore been suggested that cortisone and ACTH operate at the level of the tissues and cells.

Since the effects of salicylates in such studies are similar to those obtained with ACTH and cortisone, it would appear that their mechanism of action is similar. Kelemen and his co-workers¹⁰² reported that the administration of large doses of salicylates to animals and man stimulates the nonspecific defense mechanisms of the organism, with a resultant mobilization of the cortisone-compound F system. Small doses do not have this effect.

That the adrenal cortical hormones are concerned with the distribution of body fluids and electrolytes has been established. The administration of cortisone to normal animals may result initially in retention of water in the extracellular fluid compartment; with continued administration of this drug, water is redistributed into the intracellular phase. The daily administration of a large dose of cortisone may deplete the body's store of potassium.¹¹⁹

The observations of Kroop and Slater¹²⁰ suggest that cortisone may initiate such an endogenous shift of water in patients with acute rheumatic fever. In three children with acute rheumatic carditis treated with cortisone, distended neck veins, hepatomegaly and ascites developed within seven to 11 days, despite marked clinical improvement and an insignificant variation in body weight. The results were interpreted as indicating that corti-

sone had stimulated a shift of water from the cells into the extracellular compartment and that the associated increase in blood volume, in the presence of myocardial damage, had produced congestive failure. Since the serum electrolyte concentration was maintained, the authors felt that there was also a shift of intracellular electrolytes to the extracellular compartment. It is of interest that the development of pulmonary edema¹⁰⁸ during salicylate therapy of rheumatic fever has been previously reported and was attributed to an increase in plasma volume.

COMMENT

Assembling the various fragments in the puzzle which is rheumatic fever, it is possible to arrange them into a logical working hypothesis.

The Etiologic Bacterial Agent: There remains very little doubt today that infection with a group A beta hemolytic streptococcus precedes the development of acute rheumatic fever. Repeated infections by different types of group A streptococci may be important. The specific antigenic substance or substances common to all group A streptococci which may be responsible for the development of rheumatic fever have not been identified. Since rheumatic fever does not appear to be associated with a generalized hyperreactive immunologic capacity or with infections by other microorganisms, it is possible that group A streptococci contain or elaborate an unidentified antigen or antigens with unique immunologic properties. There are no conclusive evidences at the present time to suggest that organ-specific antibodies are involved in the pathogenesis of rheumatic fever.

The Host Factor: It is not known why only a small percentage of individuals infected with group A streptococci develop rheumatic fever. The familial incidence of this disease suggests that there is a factor of genetic susceptibility. All evidences considered, it appears as though the individual in whom rheumatic fever develops reacts in a peculiar fashion immunologically to the streptococcal infection, and that the clinical symptoms and signs are the overt manifestations of this abnormal antigen-antibody reaction.

Although data on the physiologic changes induced by the union of antigen and antibody within a living organism are still scanty, it appears that such an event profoundly alters homeostasis. Susceptibility, immunity and sensitization all seem to depend upon the activities of the cells of the reticulo-endothelial system. Recent studies have shown that antigenic substances are rapidly distributed throughout these cells. Of particular interest is the observation that even macromolecular substances are incorporated into these cells and, in particular, into the mitochondria. Mitochondria have a high enzyme content.¹²¹ They are thought to be the site of protein synthesis, and it has been suggested that antibody formation is protein synthesis modified by the presence of antigen. Whether this modification is accomplished by an enzymic adaptation is not known. It is apparent that any factor which modifies protein metabolism might also affect the immune response.

Of the cells of the reticuloendothelial system, it appears that the plasma cells are most prominently involved in antibody formation.

It is not known whether the histopathologic lesions seen in experimental hypersensitivity are the result of the intracellular localization of antigens, the development of antibodies, or the intracellular interaction of antigen and antibody. Their constant presence in such studies, however, suggests some causal relationship. The results of the recent studies suggest that the so-called antigen-antibody or hypersensitivity reaction is the result of some abnormal enzymic process occurring within certain body cells.

A clue to the nature of the abnormal response of the rheumatic subject is suggested by the observation that his antibody response to streptolysin is in general greater than that of an individual with streptococcal infection who does not have rheumatic fever as a sequel. It should be emphasized that most of these immunologic studies are based on two-dimensional measurements of the concentration of various antibodies in the blood stream. These may not accurately reflect a change in the rate of antibody production or destruction, which are intracellular functions. For instance, if the rate of antibody production and the rate of antibody catabolism are elevated equally at the same time, the extracellular concentration of antibody may conceivably remain unchanged. Likewise, if the rate of synthesis and the rate of destruction are both decreased, there still may be no change in the serum concentration. Fluctuations in the distribution of body fluids between the intracellular and extracellular compartments may produce changes in the serum concentration of antibody, even though the total body content of antibody may not be altered. It is suspected that such alterations in fluid distribution do occur during acute rheumatic fever.

Since technics are now available for determining the rate of protein anabolism and catabolism in intact animals, further information regarding this aspect of the riddle may be forthcoming. Such studies might indicate a greater difference in the rate of metabolism of antibody in rheumatic and nonrheumatic subjects than has been previously suspected.

The mechanism or mechanisms whereby cortisone and ACTH exert their beneficial effects on the clinical symptoms and signs of acute rheumatic fever are not clearly understood at present. It is generally considered that the eventual locus of effect is at the tissue level. The observation that cortisone suppresses or inhibits antibody production suggests that the administration of ACTH or cortisone effects a return toward homeostasis in the organism by altering the metabolism of protein. These agents may be considered as acting in a compensatory fashion to reduce the abnormal rate of antibody synthesis. The tendency of cortisone and ACTH to retard the healing of wounds and to suppress mesenchymal tissue reaction may be another manifestation of this fundamental effect on protein metabolism. The known effects of salicylates in rheumatic fever can also be explained on this basis.

The physiologic alterations observed, such as the changes in the distribution of body sodium during acute rheumatic fever and the loss of intracellular water during salicylate therapy, may be but reflections of the intracellular changes induced by a hypersensitivity reaction. Any stimulus which interferes with the normal intracellular enzymic functions may disrupt the unstable energy equilibrium which maintains the normal differential concentration of potassium intracellularly and sodium extracellularly. Indeed, it is thought that living cells actively extrude water against a gradient.¹²² Thus an intracellular antigen-antibody reaction may result in intracellular edema and eventually in death of the cell.

It is evident that further careful and intensive measurements of the physiologic alterations which occur during acute rheumatic fever may eventually reveal new clues as to the fundamental biologic abnormality in this puzzling disease state.

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CASE REPORTS

SERUM NEURITIS *

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NERVOUS system complications following the therapeutic or prophylactic administration of foreign serum are less widely appreciated than are the more common allergic complications, such as pain and edema at the site of injection, regional adenopathy, fever, urticaria and serum sickness syndromes. Furthermore, these neurologic complications are given little stress in standard textbooks of medicine. It is the purpose of this paper to call attention to these manifestations in the light of a report of two additional cases. One patient illustrates the most frequent type of neurologic complication, a peripheral neuritis involving the brachial plexus. The other represents the less frequent involvement of cranial nerves and is the only case involving the trigeminal nerve which we could find in the medical literature available to us.

The first report of serum neuritis has been attributed to Englemann in 1897.¹ During the first four decades of the present century the use of many antibacterial serum preparations resulted in a not infrequent occurrence of serum neuritis. In 1932 Young² reported a study of 50 cases of this disease following the administration of antisera, with tetanus antitoxin accounting for about one-half of these cases. In the same year, Wilson and Hadden² reported six cases occurring after the use of tetanus antitoxin or diphtheria antiserum. Doyle³ in 1933 reported two cases of his own and collected 47 authentic examples from the literature. In all of this latter group of cases motor function was disturbed, but in only one fourth were there sensory changes. During the past decade serum neuritis has become less frequent since use of antibiotics has virtually supplanted antibacterial sera except in the case of tetanus antitoxin.

Serum disease of the nervous system occurs predominantly in individuals over 21 years of age. There is a decided predilection for males,^{1,4} which is probably a reflection of greater liability to injury necessitating administration of tetanus antitoxin. Both the central and the peripheral nervous systems can be involved, either separately or concomitantly.

The most common type of involvement is that of the roots comprising the brachial plexus. This usually (though not necessarily) follows a serum sickness reaction and is heralded by the onset of pain across one or both shoulder girdles. The pain is followed within hours or days by the appearance of paralysis. Sensory changes are slight or absent. On the other hand, individual peripheral nerves may be affected or a polyneuritis may result from involvement

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of multiple peripheral nerves.⁵ These complications may occur without preceding serum sickness reaction, although as a rule the appearance of neuritis follows at least a local or an urticarial reaction. The predilection for the brachial plexus was attributed by Baudoin and Hervey⁶ to the low chronaxy of these nerves, but this theory is not universally accepted.⁵

The most serious forms of serum disease of the nervous system are those resulting from involvement of the central nervous system. Cerebral involvement has been reported by Kennedy⁷ and by Fisher,⁸ and is stressed in a recent publication by Park and Richardson.⁹ Other authors^{1,4} refer to spinal cord involvement, a complication which usually follows intrathecal administration of the serum preparation. In the above types of disease the clinical picture and physical findings depend upon sites and severity of activity. Hemiplegia, paraplegia, aphasia and coma may result.

Cranial nerves may also be involved. The second, third, seventh, ninth, tenth and eleventh nerves have been reported as being involved, either alone or in combination with other complications.^{1,4} Cutter¹⁰ reported involvement of the auditory nerves, and labyrinthine damage has also been mentioned. As far as we can find, our second case represents the first report of trigeminal nerve involvement, an occurrence all the more unusual in view of the predominant involvement of motor nerves.

Comroe and co-workers¹¹ have reported a case of brachial neuritis following administration of tetanus antitoxin, with concomitant involvement of the muscles of respiration. This patient eventually recovered completely.

The basis for the neurologic involvement is generally considered to be similar to the basis for other types of serum reaction, namely, hypersensitivity. Since both nervous system and skin are ectodermal derivatives, it is not unreasonable to assume that nerves can develop edema similar to the urticaria which occurs in the skin. Edema of a tightly bound nerve trunk can understandably lead to impairment of function. Moreover, the causative edema may occur at a spinal foramen, or at any canal through which a nerve courses. Kraus and Chaney⁴ describe in detail the pathologic changes in the nervous system resulting in experimental animals subjected to anaphylactic shock. These findings lend further strength to the impression of hypersensitivity reaction.

The prognosis in instances of serum disease of the nervous system is generally good. Complete recovery of function may occur even in instances of central nervous system involvement. Occasionally either partial or total permanent paralysis of a muscle or of several muscles may persist.

Treatment during the acute phase consists of the treatment for serum sickness in general, and consists of rest, dehydrating agents, epinephrin and the use of antihistamine drugs. Vitamin B complex, particularly thiamine, may also be of value. The success of ACTH and cortisone in treatment of other diseases of allergic basis suggests there may be a place for the use of these drugs in treatment of serum neuritis also. Fetter¹² recently reported a case of serum neuritis treated with these drugs; although there was prompt relief of coexistent arthralgia, the neuritic manifestations subsided slowly. The effect of cortisone in this instance is difficult to evaluate since spontaneous recovery is almost the rule in this disease. Walsh¹³ described the failure of cortisone therapy to expedite improvement in a case manifesting signs of brachial plexus and central

nervous system involvement. Following the acute phase, physiotherapy is indicated for muscle groups which are tardy in recovery.

CASE REPORTS

Case 1. A 27 year old white man suffered a puncture wound of the sole of the left foot from a rusty nail on August 7, 1948, and within three hours had been given a "tetanus injection," presumably tetanus antitoxin, in the left deltoid region. Five days later he noted swelling of the left axillary nodes, and eight days after the injection developed severe pain in the left shoulder which radiated across into the right shoulder. Later that day he noted the onset of weakness of the left shoulder and arm. Two days later weakness developed in the right arm. At the time of admission to the hospital, 12 days following the injection, he complained of little pain but sat with his arms hanging limply in his lap. Partial atrophy of the deltoid muscle was noted bilaterally, and there was a shoulder drop on the left. Mild spasm of the trapezius was noted on the left. The biceps reflex was markedly diminished on each side; "partial" paralysis of the upper extremities was noted bilaterally, more marked on the left. The sensory examination was completely normal.

Complete blood count, urinalysis, serologic tests for syphilis, chest x-ray and fluid examination all showed normal findings. Agglutinations for specific fevers showed the following positive findings: (1) the typhoid agglutination was positive in a dilution of 1:20 for both O and H antigens; (2) a heterophil agglutination was positive in a dilution of 1:56, later falling to 1:14; (3) the tularemia agglutination was positive, the titer varying from 1:320 to 1:640.

For the first hospital week the patient complained occasionally of slight pain in the shoulders, but thereafter was pain free. During a 45 day hospital course he was given physiotherapy and showed progressive increase in strength in both shoulders and arms until eventually there were no apparent residuals of the previous neuritis. The patient was discharged from the hospital with no complaints.

Case 2. A 31 year old white man entered the hospital on June 29, 1951. Six weeks prior to admission he had received a puncture wound of the right hand and was subsequently given an injection of tetanus antitoxin. Several days thereafter he developed serum sickness, with fever, marked malaise and generalized lymph node swelling, particularly the cervical and submandibular nodes. This was accompanied by aching in the joints and muscles of the extremities; urticaria also appeared. This was followed in several days by pain in the right face and jaw which was of two types: (1) a persistent dull aching pain felt in the region of the right parotid gland and along the right mandible; (2) periodic episodes of excruciating pain, beginning suddenly in the right parotid area and radiating forward to involve the entire right side of the face. This severe pain lasted 10 to 20 minutes, after which it subsided gradually, only to reappear periodically. Occasionally, chewing precipitated paroxysms of pain. No treatment had been administered except applications of heat to the face.

Physical examination disclosed no abnormalities except an anal fistula. No trigger areas were noted on the face or buccal mucosa.

Complete blood count, urinalysis, serologic tests for syphilis and chest x-ray were all within normal limits.

The patient was seen in consultation by an otolaryngologist, who could find no overt cause for the pain and concurred in the impression of serum neuritis with trigeminal neuralgia. During the first week in the hospital the patient continued to have dull aching pain throughout the right side of the face but experienced none of the severe neuralgic episodes. He was treated with rest, sedation, vitamin B complex and thiamine. After one week he was entirely pain-free. Subsequently he was

transferred to the Surgical Service, where the fistula-in-ano was excised, and he was discharged from the hospital. Follow-up examination eight months later disclosed no complaints.

COMMENTS

Our first patient showed the common type of neurologic involvement, with peripheral neuritis due to involvement of the brachial plexus. The positive tularemia agglutination in this patient requires comment in that it possibly represents an anamnestic type of reaction. Although the patient gave no history of tularemia, this is a not uncommon disease in the rural area surrounding Memphis. In the second case the diagnosis of trigeminal neuralgia was made on the basis of the patient's subjective manifestations; these complaints were thought to be typical.

In this disease, as with other diseases, ideal treatment consists of prevention. Since, currently, serum neuritis is seen almost exclusively following the administration of tetanus antitoxin, it is not unreasonable to expect, with the widespread use of tetanus toxoid immunization in pediatric practice and in the Armed Forces, that eventually this source can be eradicated. Patients being given tetanus toxoid should be informed of the nature of the injection, and physicians confronted with an indication for the use of tetanus preventive would do well to question their patients regarding previous immunization with toxoid. If the patient has had no previous immunization, tetanus antitoxin should be used after appropriate tests for sensitivity. On the other hand, if the patient has been previously immunized with tetanus toxoid, a booster dose of the latter is the treatment of choice and would obviate the possibility of serum neuritis. The problem of how long a time lag may be permitted from previous toxoid immunization to booster dose is a difficult one to answer. McBryde and Poston,¹⁴ in a study of a group of colored children given basic immunization with alum precipitated tetanus toxoid, found that even at intervals of five years following the original immunization, a dose of 0.1 c.c. of tetanus toxoid intradermally, or 0.5 c.c. of the toxoid subcutaneously, seemed effective in producing a satisfactory booster response. In practice, however, it is better that this booster injection be given at an interval no longer than about two and one-half years, at which time it was found by these investigators that 0.1 c.c. intradermally was probably the smallest practical booster dose.

McBryde and Poston also commented upon the fact that as small a booster dose as 0.004 c.c. at an interval of two and one-half years produced a satisfactory response in all of six individuals so tested. In view of this it was questioned whether a stimulating dose was actually necessary, since it has been theorized that the toxin elaborated by a tetanus infection would possibly act as a satisfactory mechanism. To be safe, one should give tetanus toxoid booster doses either at routine intervals or on the occasion of an injury in which there is thought to be a possibility of tetanus infection. No severe reactions were encountered by these workers with the use of toxoid.

SUMMARY

The occurrence of serum disease of the nervous system is a relatively infrequent complication of the administration of foreign serum. Two additional

cases are reported, one of which manifested brachial plexus involvement and the other trigeminal neuralgia. The latter apparently constitutes the first such report in the literature. This disease usually—but not necessarily—follows an allergic reaction of other type, and involves predominantly the peripheral nervous system, but also, much less frequently, the central nervous system. Serum neuritis is thought to have an allergic basis. The prognosis is generally good and treatment is the same as for hypersensitivity reaction of other types, plus the use of physiotherapy when necessary. Mention is made of technics of tetanus toxoid immunization.

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**PERSISTENT HYPERLIPEMIA AND HEPATOSPLENOMEGALY
IN A PATIENT WITH CONTROLLED DIABETES
MELLITUS***

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HYPERLIPEMIA has been shown to occur in association with a number of disease states.^{1a} Movitt et al.² and Thannhauser^{1a, b} have listed the conditions, and Thannhauser has written an excellent monograph on the lipidoses.^{1a}

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One of the disease states with which hyperlipemia is associated is diabetes mellitus.^{1a, b, 3, 4, 5} Thannhauser states,^{1a} however, that the hyperlipemia of diabetes "is controlled completely by insulin." Carfagno and Steiger,³ in reviewing 63 cases of lipemia retinalis in the literature, to which they added one of their own, state that lipemia retinalis was seen in the diabetic patients only when they were in acidosis. They observed that the majority of the patients were young male diabetics. In all of the published reports of hyperlipemia associated with diabetes mellitus that they reviewed in which the patients were adequately studied, the degree of lipemia varied with the blood sugar levels and disappeared or was markedly reduced when the diabetes was controlled, as reflected in the blood sugar levels and the absence of acidosis.³ Lawrence⁶ reported a case of hyperlipemia associated with diabetes mellitus in which there was associated hepatosplenomegaly. The patient was a 33 year old woman who developed over a period of seven years "complete lipodystrophy, a huge liver and spleen, and enlargement of the parotids and all the lymph glands." A low fat diet was not tried in Lawrence's patient, but it was noted that the lipemia varied in degree with the state of control of her diabetes, becoming more marked if the diabetes was not well controlled. Lawrence feels that with long standing hyperlipemia and associated diabetes, "the spleen may become enlarged and contains from the accumulation of cholesterol esters or some closely akin lipid in the reticuloendothelial cells, the so-called 'foam cells' very like the cells found in Gaucher and Niemann-Pick type of splenomegaly." The liver showed portal cirrhosis at autopsy. The fat content of the liver and all the internal organs was normal. The diabetes was extremely insulin-resistant. Other workers^{7, 8, 9} have noted large cell hyperplasia in the organs of patients with severe diabetes.

Hyperglycemia and glycosuria have been described as occurring as a part of the picture of essential hyperlipemia,^{1, 2, 13} and in chronic relapsing pancreatitis there may be hyperlipemia and glycosuria,^{1a, 2, 13} the latter finding in particular being transient unless the pancreas becomes so damaged that permanent diabetes results.^{10, 11, 12} In patients with essential hyperlipemia, lowering of the blood lipid level and disappearance of the hyperglycemia and glycosuria could be accomplished by a low fat diet^{1a, b, 13} but not by insulin.^{1a} In differentiating essential hyperlipemia from that due to diabetes, Thannhauser states^{1a}: "... it has to be stated again and again that this type of idiopathic hyperlipemia is in its pathogenesis entirely different from hyperlipemia secondary to severe untreated diabetes." He also remarks^{1a}: "no case has been observed where glycosuria accompanying primary idiopathic hyperlipemia has developed into a more or less definite diabetic disturbance requiring insulin treatment."

It seems clear, then, that (1) the hyperlipemia of diabetes mellitus can be controlled by adequate control of the diabetes, low fat diet having no effect; and (2) that the hyperglycemia and glycosuria of idiopathic or essential hyperlipemia does not respond to insulin but does respond to a low fat diet.

It is the purpose of this paper to present a case of hyperlipemia with hepatosplenomegaly in a patient with controlled diabetes mellitus in whom the hyperlipemia responded to a low fat diet.

CASE REPORT

A 52 year old white woman was admitted to the Metabolic Ward of the Philadelphia General Hospital on May 7, 1952, for study. She was first seen in the clinics

of this hospital in 1933. At that time she was treated for known diabetes mellitus of three years' duration. Her only subjective symptoms at that time were polydipsia and polyuria. Her diabetes was controlled by diet alone. Highest sugar recorded was 166 mg. per cent. There was a history of amenorrhea and obesity following the removal of her tubes and ovaries in 1918 because of "infected tubes." She complained of hot flashes, nervousness and sweating, which symptoms were presumed to be due to the surgically induced menopause. She noted occasional ankle edema and dyspnea on exertion. Electrocardiogram at that time was normal. Blood pressure was 140/90 mm. of Hg. Physical examination was negative save for obesity. The liver and spleen were not palpable.

In the interval from 1933 to the present admission, she was followed in the medical and diabetic clinics of this hospital and also had a total of 14 ward admissions as follows: three times for investigation of right upper quadrant pain, twice for relief of menopausal symptoms, five times for vaginal bleeding requiring dilatation and curettage, once for removal of a lipoma of the breast, and three times for minor ailments unrelated to the present illness. Her obesity and hypertension persisted through all admissions, the hypertension becoming progressively more marked. She also developed signs of arteriosclerosis by retinal examination.

By 1939 her diabetes required a total daily insulin dosage of 100 to 120 units, using varied proportions of protamine zinc insulin and crystalline insulin, globin insulin being substituted later for protamine zinc insulin. In 1945 her diabetes was adequately controlled by 40 to 80 units of globin insulin a day. Blood sugar levels during clinic visits and hospitalizations varied from 100 to 300 mg. per cent, including fasting and two hour postprandial specimens. Serum CO₂ combining power was always above 40 vol. per cent. No acetoneuria was ever noted.

By 1945 the dyspnea on exertion which had been continuously present became severe, and the patient also began to notice palpitation and complained of two-pillow orthopnea and occasional attacks of paroxysmal nocturnal dyspnea. Two years later she developed precordial pain which was not necessarily related to exertion. It was worse at night and was associated with pain in the left shoulder and arm and hand. X-rays of the cervical spine, left shoulder and hand were negative. The electrocardiogram, which had been normal in 1933, showed ST-T changes in 1947 consistent with a clinical impression of coronary insufficiency. An orthodiagram in 1947 described the heart as being at the upper limit of normal in size. Chest x-ray was reported as being negative. Blood pressure determinations remained consistently elevated, varying from 160/80 to 220/110 mm. of Hg, with the diastolic usually ranging from 90 to 100 mm. of mercury.

Gastrointestinal symptoms began in 1939 and were characterized by right upper quadrant pain and intolerance to fatty foods, with postprandial distress occasionally relieved by antacids. Ten years before the present admission the liver was noted to extend 6 cm. below the right costal margin, and five years later the spleen was noted to be palpable 4 cm. below the left costal margin. She was not in congestive failure at the time these observations were made. Repeated studies of the gastrointestinal tract, including two upper gastrointestinal x-rays, a barium enema, two cholecystograms, and films of the thoracolumbar spine, revealed only minor changes of hypertrophic arthritis in the lower thoracic vertebrae.

In hospitalizations prior to her present admission the patient's endocrine status was periodically investigated because of persistent and repeated episodes of postmenopausal bleeding which required five admissions for dilatation and curettage. Pathologically, endometrial hyperplasia and polyp formation without evidence of malignancy were demonstrated. It was felt that these changes were adequately explained when it was discovered that she had been taking large doses of Theelin and Premarin for menopausal symptoms. Twenty-four hour urine on her present

admission revealed urinary estrogens per 24 hours to be less than 13 mouse units; 17-ketosteroids, 6.6 mg.; gonadotropins, 0 mouse units.

Because of the symptoms and signs of obesity, hypertension, diabetes mellitus, and a suggestion of masculinizing features, skull films were taken in 1939 and 1947, and were normal on both occasions. To further rule out myxedema, suggested by the obesity and hypercholesterolemia, a basal metabolic rate was determined in 1947 and was recorded as plus 36 per cent. The test was repeated on the present admission and was minus 15 per cent.

Since 1947 random blood specimens had shown marked turbidity of the serum, and it had been noted to be "creamy" on several occasions. No fat determinations were performed, nor was the patient placed on a low fat diet. Serum cholesterol levels varied from 306 mg. per cent to 398 mg. per cent, with 60 per cent esters in each instance. Liver function studies, including cephalin and thymol flocculation, thymol turbidity, bromsulphalein retention, serum protein and albumin/globulin ratio, serum bilirubin and prothrombin time, have been done repeatedly since 1947 and have always been normal. A punch biopsy of the liver in 1949 revealed glycogen and fat deposition.

The patient was re-admitted on May 7, 1952, for study of her lipid metabolism in view of the persistent obesity, fatty food intolerance, hypercholesterolemia, hyperlipemia and recurrent lipomata. On admission her chief complaint was pain involving the left arm, with painful limitation of motion at the shoulder, and painful swelling of the dorsum of the left hand. She complained, in addition, of abdominal pain similar to that noted on previous admissions and of occasional attacks of palpitation accompanied by syncope and shortness of breath. Positive physical findings included obesity and android facies and habitus, with broad shoulders and narrow hips. No hirsutism was noted. Blood pressure was 190/80 mm. of Hg. Funduscopy revealed the salmon-pink blood vessels of lipemia retinalis. There was cardiomegaly, and a grade III precordial systolic murmur was present. There were frequent extrasystoles. The liver was enlarged to 12 cm. below the right costal margin, and the spleen was felt 4 to 6 cm. below the left costal margin. A mass 4 cm. in diameter which descended with inspiration was noted below the liver edge on the right. Neurologic examination revealed absent knee and ankle jerks, and some diminution of position and vibratory sense in the feet.

The laboratory data were as follows: Hemoglobin 14.7 gm.; white blood cells 5,000, with a normal differential; blood urea nitrogen 16 mg. per cent; CO₂ combining power 44 vol. per cent; fasting blood sugar 155 to 242 mg. per cent; two hour post-prandial blood sugar 209 to 268 mg. per cent.

Serologic test for syphilis negative; total protein 6.8 gm. per 100 c.c.; albumin 4.7 gm. per 100 c.c.; globulin 2.1 gm. per 100 c.c.

Prothrombin time 42 per cent to 100 per cent; bromsulphalein retention 3 per cent in one-half hour; cephalin flocculation 1 plus in 48 hours; thymol turbidity 10.5 units; thymol flocculation 1 plus; serum lipase 0 ml. (normal value, less than 1.5 ml.); serum amylase 62 units (normal value, less than 200 units); bleeding time 2 minutes 35 seconds; clotting time 5 minutes 15 seconds.

X-ray examination of the entire gastrointestinal tract was normal. X-ray for pancreatic calcification was negative. Intravenous pyelogram revealed minimal hydro-nephrosis on the right. Skull films were negative. Films of the cervical and lumbosacral spine showed minimal hypertrophic osteoarthritis of the lower thoracic spine. X-rays of the hands showed early rheumatoid changes. Chest films and orthodiagrams suggested left ventricular enlargement.

Liver biopsy showed fatty infiltration and fibrosis. Gastric analysis on this admission, as in 1947, failed to reveal any free hydrochloric acid. Urinalysis showed no acetone, though sugar was spilled intermittently. There was 1 to 2 plus albuminuria. One 24 hour urine sugar determination revealed 2.2 gm. of sugar.

Examination of a three day stool specimen showed a stool weight of 1,177 gm. Total stool nitrogen was 5.18 gm., and total stool lipids in terms of fatty acids was 10.12 gm. These findings were interpreted by Dr. M. S. Lopusniak, of the Graduate School of Medicine, University of Pennsylvania, as being within normal limits, and as being good evidence that there was no disturbance of the excretory function of the pancreas.

Serum turbidity studies performed with the Klett turbidometer showed that the fasting level was 182 units, which was five to six times normal; and following a meal of 189 c.c. of 22 per cent cream, the two hour level was 292 units and the five hour level was 259 units. This curve is abnormal, as the fasting two hour and five hour levels are considerably elevated as compared to a previously reported series.¹⁶ A heparin test on the effect of 100 mg. of heparin intravenously on the serum turbidity failed to reveal any clearing of the serum.

Bone marrow showed a myeloid/erythroid ratio of 3:1, with a normal maturation of erythrocytic and granulocytic series. No "foam cells" were noted.

TABLE I

	Cholesterol (normal 150-260 mg. % 70-75% esters)	Fatty Acids (normal 200-450 mg. %)	Phospholipids (normal 225 mg. %)	Neutral Fat (normal 0-200 mg. %)
1947	367-60% esters			
	398			
1948	306-60% esters			
1951	374-65% esters			
1952				
May*	644	3780	842.5	2711.7†
June		1160	660	
August		629	368.8	

* Patient was placed on a 30 gm. fat diet after these initial determinations.

† Calculated from the formula of Thannhauser and Reinstein¹⁷: Fatty acid minus (0.72 cholesterol ester plus 0.69 total phospholipid) \times 1.04 equals neutral fat. In this instance, however, the cholesterol ester was not determined and the figure for the total cholesterol was used. The actual value for neutral fat, then, must be much higher.

During most of her hospital stay the patient complained of intermittent epigastric pain that was aggravated by dietary indiscretion and was somewhat relieved by the administration of dilute hydrochloric acid. The pain in her hand persisted in spite of the administration of 30 micrograms of vitamin B₁₂ every day. It was felt that the arm changes either were due to diabetic neuropathy or represented a reflex dystrophy secondary to coronary artery disease of the type well described by Steinbrocker.¹⁴ No ganglionic blocking agents were tried in an effort to relieve the pain. On May 19, 1952, the patient experienced the sudden onset of dyspnea and ataxia and began to perspire profusely. Her heart rate was noted to be 160 per minute, with a completely irregular rhythm, and the diagnosis of paroxysmal auricular fibrillation was confirmed by electrocardiogram. Electrocardiogram before the attack, taken on admission, had shown a normal sinus rhythm with ST segment depression in Leads I, II, aVL, and V₁ to V₆. The patient was digitalized, with restoration of a normal sinus rhythm and cessation of attacks.

Her diabetes was controlled with injections of 35 units of globin insulin in the morning and 15 units at night. Because of her coronary artery disease no attempt was made to keep fasting sugars below 160 mg. per cent, and hers varied from 155 to 242 mg. per cent, and her two hour postprandial sugars from 209 to 268 mg. per cent. The urine remained free of acetone.

Because her hyperlipemia failed to respond to adequate control of her diabetes, and because it was felt that this patient might have essential hyperlipemia entirely unrelated to her diabetic state, in May, 1952, she was placed on a diet containing 30 gm. of fat per day. She adhered to the diet rigidly, both in and out of the hospital. She was also given choline, 3 gm. twice a day. On this régime the hyperlipemia cleared markedly, as can be seen from table 1. The patient lost 30 pounds in weight in the three months on the diet. The hepatosplenomegaly persisted, but the spleen was only slightly enlarged. She has had fewer episodes of epigastric distress and the angina has remained unchanged.

COMMENT

Hyperlipemia in the presence of hyperglycemia and glycosuria suggests diabetes mellitus, idiopathic or essential hyperlipemia, or primary pancreatic disease. The hyperlipemia of diabetes mellitus, however, is eliminated or markedly reduced by control of the diabetes. It is usually associated with acidosis and is seldom associated with marked hepatosplenomegaly. It is not altered by feeding a low fat diet. Essential hyperlipemia may be accompanied by hyperglycemia and glycosuria, but both the hyperlipemia and the hyperglycemia respond to a low fat diet, and neither responds to insulin. The hyperlipemia noted in acute or chronic pancreatitis may be accompanied by elevation of the blood sugar level, but, once again, cure of the pancreatitis results in disappearance of the hyperglycemia unless the pancreas is so damaged over a period of time that permanent diabetes develops. In such an instance, one would expect to find other evidence of pancreatic disease.

Movitt et al.² noted an increase in the serum lipids prior to attacks of abdominal pain in patients with essential hyperlipemia and were able to predict attacks of pain on this basis. More recently, Klatskin and Gordon¹⁸ presented a case and reviewed the literature on essential hyperlipemia. These authors and Poulsen¹⁹ present evidence that the attacks of abdominal pain in this disease are due to a secondary relapsing pancreatitis brought on by the hyperlipemia. The attacks in Klatskin and Gordon's patient were prevented by a low fat diet, and the hyperlipemia decreased markedly. Both the hyperlipemia and the attacks recurred when the patient resumed a diet with normal fat content. A comparison of our case with the cases which Klatskin and Gordon reviewed is presented in table 2. It can be seen that our patient presents many features highly suggestive of essential hyperlipemia.

This patient presents several features which, if she has essential hyperlipemia, are unusual. First, her disease is associated with diabetes mellitus, a disease itself known to be associated with hyperlipemia. Second, the patient has been followed for almost 20 years, and it was not until she was 47 years old that her serum was noted to be lipemic. Of a total of 31 patients (11 of pancreatitis with lipemia and 20 of essential hyperlipemia) reviewed by Klatskin and Gordon, all but three or possibly four (the age of one was unknown) were under 40 years of age at the onset of their disease, and 14 patients were less than 20. Third, Thannhauser states¹⁸ that hepatosplenomegaly is rarely seen in the adult patient with essential hyperlipemia.

It is unlikely that primary pancreatic disease could be the cause of both the diabetes and the hyperlipemia, because the hyperlipemia of primary pancreatic

TABLE II

	Essential Hyperlipemia (Klatskin and Gordon) 20 cases	Patient A. Q.
Sex		
Male	18	
Female	2	+
Age at onset		
Under 30 yrs.	15	+
Over 30 yrs.	5	
Abdominal pain		
Present	12	
Intermittent	12	+
Xanthoma of skin	16	(?)
Lipemia retinalis	9	+
Hepatomegaly	16	+
Splenomegaly	14	+
Serum lipids		
Measured	18	+
Elevated	18	+
Neutral fat		
Measured	14	+
Increased	14	+
Phospholipids		
Measured	18	+
Increased	14	+
Cholesterol		
Measured	20	+
Increased	18	+
Lipemia between attacks—Tested	11	+
Present	10	+
Low fat diet tried	16	+
Reduced lipemia	16	+
Urine or serum amylase		
Tested	7	+
Increased	0	0
Serum lipase		
Tested	1	+
Increased	1	0
Decreased	0	0
Liver function tested	3	+
Abnormal	2	0
Liver biopsy performed	1	+(2)
Lipoidal cells	0	0
Bone marrow biopsy	2	+
Lipoidal cells	0	0

disease should be marked only during acute exacerbations of the pancreatitis, and this patient's hyperlipemia was persistent, responding only to a low fat diet.

SUMMARY

A patient is presented who has diabetes mellitus, hepatosplenomegaly and hyperlipemia. The hyperlipemia in this patient persisted in spite of what was felt to be adequate control of her diabetes. The hyperlipemia responded to a low fat diet.

It is felt that this patient probably represents a case of essential hyperlipemia in a patient with diabetes mellitus.

ACKNOWLEDGMENTS

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SUBCOSTOSTERNAL DIAPHRAGMATIC HERNIA *

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THE first recorded description of the rare anomaly variously named "para-sternal," "substernal," "anterior" or subcostosternal (Harrington) diaphragmatic hernia is found in J. B. Morgagni's book, "Seats and Causes of Diseases" (1761):

* Received for publication November 18, 1953.

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"There certainly are places in the diaphragm through which, upon drawing asunder of the fleshy fibres, and upon the giving way of the membranes, the stomach, or some part of the intestinal tube, or any other viscus, may pass over from the belly into the thorax. . . .

"Thus, also, anteriorly, betwixt the fibres that come from the xiphoid cartilage and the neighboring fibres, there generally is an interval through which something similar may happen: and I even suspected this to have happened in a husbandman in whom—I heard that Leprotti saw at Rome—part of the intestine colon carried up, through the middle and anterior part of the diaphragm, in so great a quantity as to equal a span, when extended.

"But as I afterwards heard from those who had dissected the body, that neither this intestine, nor the foramen, the diameter of which was two thumbs breadths, and through which this part went out and came in, show'd any signs of foregoing violence or disorder and that the man died in decrepit age, from a manifest injury within the skull, I chose rather to suppose that it had been thus from the original formation."

Thus, about 200 years ago Morgagni described the defect which permits the development of a hernia through the anterior part of the diaphragm.

DEFINITION

At present, diaphragmatic hernia is defined as a protrusion of abdominal viscera through a defect of the diaphragm into the thoracic cavity. This definition should be enlarged to include the reverse condition as well, i.e., a protrusion of the thoracic viscera through a diaphragmatic defect into the abdominal cavity. Callander, Woolsey and others have considered this theoretic possibility but denied the actual occurrence of it. We have found two cases in the literature with "reverse diaphragmatic hernia." Kilner reported a "prolapse of the lung through a deficiency in the anterior portion of the diaphragm." Lust describes a displacement of a very considerable portion of the esophagus into the abdominal cavity.

Morgagni's foramen (Larrey's space) is a triangularly shaped space between the muscular fibers of the diaphragm which are inserted at the posterior surface of the xiphoid process, and those which are attached to the cartilage of the seventh rib. These spaces, which are normally filled with loose areolar tissue, vary in size depending on the presence or absence of strong muscle fascicles. Herniae protruding through these openings usually have a hernial sac, which is an indication that they were formed after complete closure of the diaphragm (Harrington).

SYMPTOMS

Uncommon as subcostosternal diaphragmatic hernia is, it appears to be not so rare as reflected by the literature: it is usually overlooked and found only by chance, at operations or at autopsy. The symptoms in these cases depend upon the organs involved in the hernia and the disturbance of functions of these or neighboring organs through the hernial displacement. The lungs may be compressed, causing dyspnea, chronic cough and hemoptysis. The heart action as well as the intrathoracic circulation may be impeded, producing pain subternally or in the shoulder region, palpitation, a feeling of suffocation, cyanosis and weakness. After physical exertion or voluminous intake of food or liquids, these chest symptoms are especially noticed.

When the colon, the small intestines, or the stomach participate in the hernia their compression, torsion, or obstruction may cause chronic constipation, vomiting, meteorism, epigastric pain, intestinal hemorrhage, severe loss of weight, nausea, regurgitation, indigestion as in peptic ulcer, hematemesis, melena, abdominal colic, difficulty in swallowing liquids rather than solids (paradoxical dysphagia)—all, a part, or none of these symptoms may be found in patients suffering from subcostosternal hernia. It is considered characteristic that these symptoms appear intermittently and are not related to meals, although the patients state that they cannot lie down after meals. Great relief is felt after vomiting, so that some patients are known to induce vomiting, or to practice emptying of the stomach by passing a stomach tube.

DIAGNOSIS

To diagnose subcostosternal diaphragmatic hernia, the physician must "think of it" (Ruetz). This should certainly be done when a study of the stomach, gallbladder and intestines in a patient with upper abdominal symptoms does not give a satisfactory explanation for them, or when chest symptoms apparently are not based on chest pathology. Since the objective signs vary in quality and quantity, even in the same patient at different times, depending on the variable content of the hernia, their presence will invite further examinations; their absence is of no particular significance.

Inspection may reveal asymmetry of the thorax, possibly obliteration of intercostal spaces, or lag of respiratory movements on the affected side or in the costosternal angle. In hernia with a large sac and visceral content, a scaphoid abdomen may be observed.

Percussion will give a tympanic sound in the presence of large hollow organs in the chest. Displacement of the normal percussion sounds, especially in the lower parts of the thorax, or the sudden change of these sounds after drinking of water by the patient, are important findings.

During *auscultation* intestinal borborygmi will occasionally be heard over the chest. They are—when eventration can be excluded—pathognomonic. Metallic tinkling sounds (pulmonary compression) with respiratory movements, or gurgling sounds (air or fluid in intestines) independent of respiration, are often noticeable.

A very common finding is the displacement of the heart, mostly to the right, by a large subcostosternal diaphragmatic hernia. This dextrocardia is sometimes accompanied by a systolic murmur—due to kinking of large vessels (Eppinger) or to associated congenital heart disease (Guttman)—bradycardia and arrhythmia. All these physical signs are changeable in this type of diaphragmatic hernia because of the varying content of the colon within the hernia.

While the usual means of clinical examination may give the physician a strong and justified suspicion of the presence of diaphragmatic hernia, *roentgen examination* in Trendelenburg's position alone will permit diagnosis with reasonable certainty. The flat plate of the chest may show localized areas of rarefaction or increased density in the sternodiaphragmatic angle. Occasionally the haustrations of a loop of air-filled colon may be seen in the chest.

Filling of the intestinal tract by contrast media will give further evidence of the presence of abdominal viscera in the thorax. If this method of visualization fails, the possibility of a spontaneous reduction of the hernial contents or the pres-

ence of the omentum or liver as the sole abdominal organs within the sac must be considered. This most valuable examination should be used in a newborn with cyanosis and dextrocardia, in the case of complete or partial intestinal obstruction of inexplicable cause, and in a person with a history of severe chest injury. *The basic requirement* for a diagnosis of diaphragmatic hernia of any type is to demonstrate the presence of abdominal viscera in the thoracic cavity.

DIFFERENTIAL DIAGNOSIS

When physical or roentgenologic deviations from the norm are detected within the chest, a number of diseases must be ruled out in differential diagnosis. In eventration, abdominal viscera are displaced cephalad, but the diaphragm is intact and continuous in its outline. Phrenic nerve stimulation (Jamin) or pneumoperitoneum before roentgen examination may help in visualization of the diaphragm.

Pneumothorax, with or without fluid, shows air extending to the dome of the pleural cavity. In subcostosternal hernia one finds circumscribed gas pockets just above the diaphragm, mostly in the cardiophrenic angle, and displacement of the heart. Pleurisy, with or without exudate, and pulmonary tuberculosis with cavities can be differentiated by their history, course and x-ray findings, although the physical signs may be similar to those of diaphragmatic hernia. An increased circumscribed density in one of the lower lung fields "justifies the clinical diagnosis of a primary intrathoracic lesion—possibly a tumor" (S. W. Harrington). A roentgenologically normal gastrointestinal tract would seem to confirm this belief; however, the possible occurrence of a diaphragmatic hernia with omentum in the sac must be kept in mind.

Feeding problems in very young children, with vomiting, abdominal colic, failure to gain weight, and with dyspnea and cyanosis during feeding, can be due to several different causes, e.g., congenital heart disease, atresia of the esophagus with tracheal communication, etc. X-ray examination with a small quantity of barium or lipiodol, or with introduction of a radiopaque Levine tube, will differentiate these diseases from another possibility, diaphragmatic hernia. In this same manner, gastric or esophageal diverticulitis, cardiospasm, hour-glass stomach, cancer of the stomach, perforation of the esophagus, peptic ulcer and gall-bladder disease may be identified and their symptoms, which may be similar to those of diaphragmatic hernia, properly accounted for.

True pectoral angina, as well as so-called pseudoangina, giving rise to chest or epigastric pain—especially after meals—differs from those produced by diaphragmatic hernia in their location (mainly in the chest) and in their direct connection with physical effort or spells of nervous excitement. However, diaphragmatic hernia may coexist with any of the above named diseases, which causes frequent diagnostic errors. "The clinical diagnosis of diaphragmatic hernia is usually uncertain" (Hedblom).

ERRORS

Errors in diagnosing diaphragmatic hernia are as numerous and as diverse as the many conditions which have to be considered or excluded in the differential diagnosis. The 198 cases of esophageal hiatus hernia collected by S. W. Harrington had had an average of three erroneous diagnoses previously. Twenty-three of these cases were operated upon primarily for other conditions. When

only omentum is present in the sac of a subcostosternal hernia, it is often considered to be an intrathoracic tumor. This error is especially apt to be made when neither symptoms nor radiologic findings point to a pathologic process in the abdomen.

In 1951 Saltzstein et al.¹⁰ collected 45 cases of subcostosternal herniae (published by different authors between 1921 and 1949), from which we quote 12 cases, interesting because of previous errors in diagnosis (table 1).

To this series we add another case of subcostosternal hernia previously diagnosed erroneously.

TABLE I

Author	Age Sex	Content of Hernial Sac	Side	Diagnosis Through	Previous Diagnosis
Eerland 1946	12 yrs.	Liver only	Right	Operation	Dermoid of anterior mediastinum
Landivar 1947	34 yrs. Male	Omentum only	Right	Operation	Pulmonary hydatidosis
Landivar 1947	50 yrs. Female	Omentum only	Right	Operation	Hydatidosis
Althabe 1944	30 yrs. Female	Loops of colon	Right	X-ray	Gall-bladder colic
Rocha 1944	46 yrs. Female	Ascending colon	Right	X-ray	Hydatid cyst at base of right lung
Ellinger 1939	39 yrs. Male	Transverse colon	Right	X-ray	Emphysema
Funk-Brentano 1933	70 yrs. Female	10 cm. of transverse colon	Right	Autopsy	Pneumonia
Colmers 1941	77 yrs. Female	Omentum and colon	Right	Autopsy	X-ray diagnosis: encapsulated effusion. No contrast meal
Landivar 1947	72 yrs. Male	Omentum and colon	Bilateral	Operation	Operation for peptic ulcer of duodenum. Both sacs spontaneously reduced, empty at operation
Reich 1922	77 yrs. Female	Omentum and colon	Right	X-ray	Ovarian cyst
Saltzstein et al. 1949	68 yrs. Male	Transverse colon and $\frac{1}{2}$ of stomach, omentum	Right	Operation	X-ray diagnosis: bronchogenic cancer of right lung
Ellinger 1939	66 yrs. Female	Transverse colon, $\frac{1}{2}$ stomach and omentum	Right	X-ray and autopsy	Diagnosed 2 yrs. previously, but pt. was asymptomatic, without stomach in sac. Complete obstruction later, died in three days

CASE REPORT

A 40 year old married salesman complained of recurrent attacks of severe pain substernally and in the left side of his chest, shortness of breath, heart palpitation, weakness, loss of weight (20 pounds in the last year), a constant feeling of fullness in the chest and abdomen, chronic constipation, and belching and gurgling sounds in the abdomen and chest. There had been no vomiting or black stools.

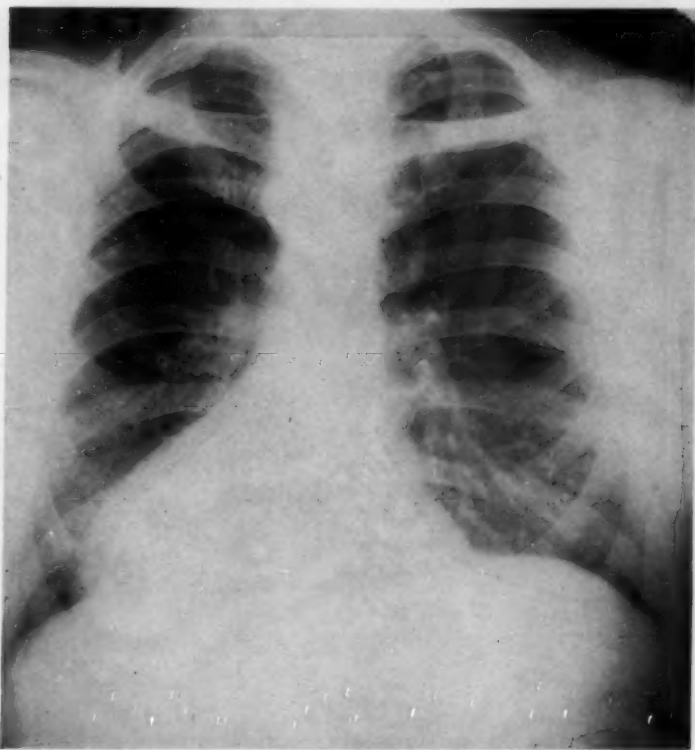


FIG. 1. Radiogram of the chest taken in the postero-anterior upright position at 77-inch focal distance shows that the shadow of the heart is markedly enlarged, with sharp outlines. Both halves of the diaphragm are normal in outline. This radiogram is completely misleading insofar as it shows no evidence of any diaphragmatic hernia.

Family History: Father died of diabetes, mother and brother of coronary thrombosis.

Past History: Negative except for chronic constipation and painful rectal spasms in 1931. Venereal diseases denied.

Present Illness: For several years the patient had suffered from the above-mentioned complaints, especially from severe pains under the sternum and in the

upper abdomen one or two hours after meals. He was often bloated, and belching gave him only moderate relief.

Excitement increased the pain in his chest. He slept poorly except when he rested on two or three pillows.

His medical attendant had told him that he suffered from "heart disease" and



FIG. 2. Lateral view of the chest in the upright position shows that the anterior mediastinum is somewhat wider than normal, and the costopericardial angle is obscured by a soft tissue mass representing the part of the transverse colon above the diaphragm.

that the fluoroscopic examination disclosed an "enlarged heart." Roentgen examination of the gall-bladder was negative except for retarded emptying.

Physical Examination: Nervous, voluble, rather drawn-looking man. Skin: pale. Tongue: coated. Eyes: Pupils react to light and accommodation. Patient wears glasses. Knee jerks: positive, equal. Romberg: negative. Lungs: no diminished resonance; bronchitic rhonchi throughout. Heart: limits not definitely ascertainable by percussion; sounds very muffled. Pulse: 76, regular. Blood pressure:

90/60 mm. of Hg. Electrocardiogram: inverted T_4 ; otherwise within normal limits. Abdomen: soft; epigastrium tender to pressure. Rectal examination: anal spasm; prostate moderately enlarged, tender to palpation. Urine: albumin, negative; sugar, positive, faint trace. Blood count: red blood cells, 4.7 millions; hemoglobin, 92 per cent (15.5 gm.); white blood cells, 5,800; neutrophils, 52 per cent; eosinophils, 1 per cent; lymphocytes, 42 per cent; monocytes, 5 per cent; Wassermann test negative; blood sugar, 109.9 mg. per cent.

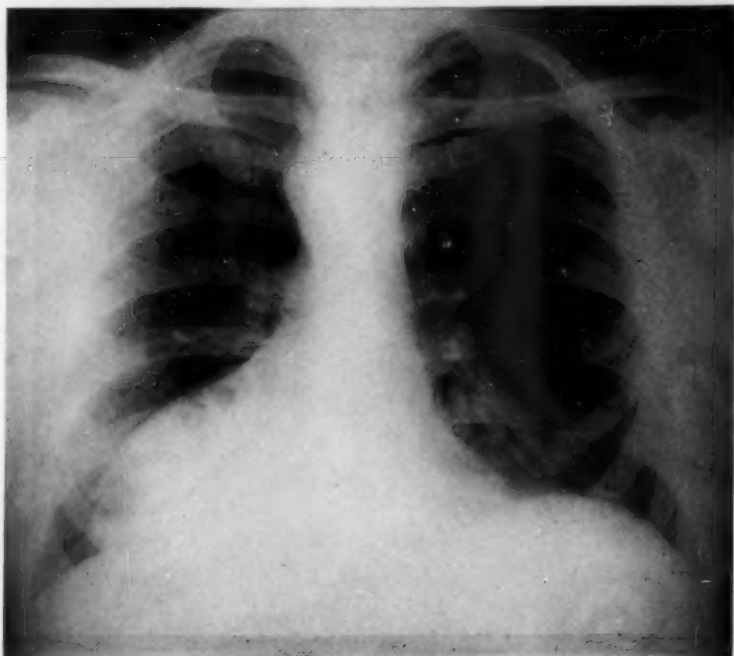


FIG. 3. During the course of examination some gas accumulated in the colon, and now on the radiogram of the chest one can see the haustral markings along the left superior border of the heart. This radiogram alone is of value in making a diagnosis of diaphragmatic hernia.

Diagnosis was deferred. We felt that since numerous symptoms in this case pointed to the digestive organs—his coated tongue, tenderness in the epigastrium, loss of weight, chronic constipation, belching and rumbling in his abdomen, anal spasm—a thorough roentgen study of his gastrointestinal tract was necessary.

Report of X-ray Examination (figures 1 to 6): There was no evidence of any abnormality in the outline of the esophagus, the stomach or the duodenum. The stomach was empty after six hours, and the meal expelled showed an irregular intestinal motility. At the end of 24 hours there was an irregular distribution of the meal in the colon. The transverse colon was partly herniated into the thorax through an opening anterior to the heart, and was situated between the latter and the anterior wall. Part of the herniated transverse colon was running along the left border of the

heart, taking up the shape of the latter and enlarging the shadow of the heart. The excursion of both diaphragms was normal and synchronized. The movement of the transverse colon was very limited, suggesting adhesions to the mediastinum.

Further examination by barium enema showed that the parts of the loops of the transverse colon located in the hiatus of the hernia were moderately narrowed. During the fluoroscopic examination a temporary obstruction to the flow of the barium was encountered at the hiatus of the hernia.

Diagnosis: Herniation of the transverse colon into the anterior mediastinum.



FIG. 4. After a complete gastrointestinal examination, including a barium enema, the portion of the transverse colon protruding into the thorax can be seen.

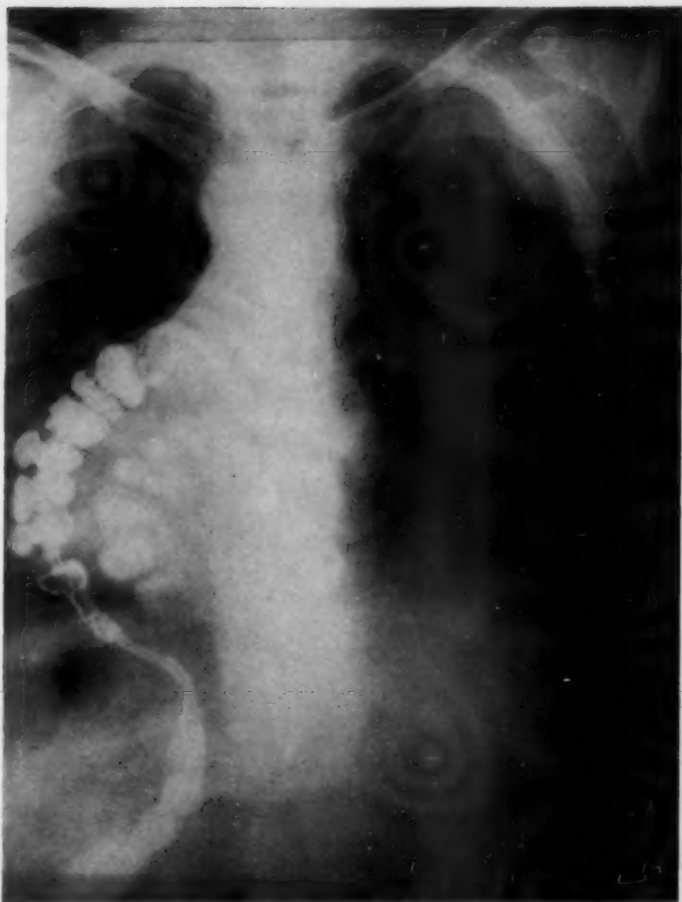


FIG. 5. A focused radiogram of the supradiaphragmatic portion of the colon shows that the herniated part runs along the left border of the heart, increasing its apparent size.

Subsequently, the patient appeared to be greatly relieved because he had learned that he did not suffer from coronary sclerosis. He refused an operation. Mild sedatives and a bland diet kept him comfortable, although the main symptoms persisted. Several months later the patient moved away and has not consulted us since.

DISCUSSION

This case of subcostosternal diaphragmatic hernia is of interest because the previous diagnosis of arteriosclerotic heart disease seemed to be plausible—even probable—considering the apparently familial tendency to coronary sclerosis.

However, the absence of objective findings for heart disease and the presence of symptoms and signs for dysfunction of abdominal viscera permitted the correct diagnosis after x-ray examination of the gastrointestinal tract.

Prognosis: Among the complications which arise in cases of subcostosternal diaphragmatic hernia are hemorrhage, peptic ulcer, respiratory failure (in infants), emaciation and, most common, acute intestinal obstruction, mostly by



FIG. 6. Lateral radiogram of the chest after barium enema, in the upright position, reveals the presence of the subcostosternal diaphragmatic hernia. The posterior mediastinum is clear. The widening of the anterior mediastinum is possibly due to the displacement of the heart backwards by the herniated colon.

constriction of the colon by a narrow hernial ring. With these facts in mind, we should state that the prognosis in every case of subcostosternal hernia is doubtful. Hedblom states that 40 per cent of congenital diaphragmatic herniae die in the first 24 hours after birth, probably less than 50 per cent reach adult age, and only a few reach old age. Subcostosternal hernia has a somewhat better prognosis, although the disability caused by it may be great. Hedblom reports the

case of a 48 year old man with double subcostosternal hernia in whom x-ray examination before operation demonstrated the presence of transverse colon in the hernial sacs. At operation, both sacs were found empty. Spontaneous reduction is most common in esophageal hiatus herniae, but it may occur also in subcostosternal herniae.

Indication for Surgical Treatment: "The treatment of diaphragmatic hernia is surgical repair of the hernial opening" (Hedblom). With this statement S. W. Harrington, Saltzstein and others agree. Saltzstein et al. state that operation would prevent the stomach from entering the chest in later life and causing sudden pyloric obstruction. Without disagreeing with this advice, we like to mention the fact that many of these patients are symptomless, that they live with some or no discomfort to old age, and that others experience spontaneous reduction of hernial contents. It is known that this "self-cure" is fairly constant in esophageal hiatus hernia (Hedblom). Kessler observed such reduction under the weight of two glasses of barium mixture. In the older literature, the giving of mercury by mouth for the reduction of diaphragmatic hernia is mentioned (quoted by Hedblom). Without doubt, in cases with acute or subacute intestinal obstruction, speedy surgical relief is required, as for all other cases of intestinal obstruction. When major surgery appears risky and the patient is more or less symptomless from his subcostosternal hernia, he should be instructed as to the possible occurrence of symptoms of acute intestinal obstruction, and a copy of the x-ray findings and plates should be left with him. (One surgeon suggested branding of the abdomen!)

Expectant Medical Treatment: The patient should be cautioned to avoid sudden and severe exertion, or overloading of his digestive tract with large quantities of food or liquids. He should abstain from coarse and gas-forming foods. Hedblom recommends that pregnancy be prevented or terminated. The patient should also be advised not to lie down after meals. This expectant medical treatment could possibly be enlarged upon.

Subcostosternal hernia passing through a normally present, though congenitally widened, opening in the diaphragm is usually considered to be acquired by increased abdominal pressure in middle age. Short of operation, some prophylactic benefit might be obtained medically by the administration of oxygen when dyspneic, the infusion of fluids when dehydrated, the insertion of a Levine tube for the relief of gastric distention, and possibly by temporary paralysis of the affected side of the diaphragm (injection of alcohol into or crushing of the respective phrenic nerve) to release the intestine caught in the hernial ring.

For patients without symptoms requiring quick and drastic treatment, we propose rational attempts at "taxis" of the hernia. These measures, mostly untried so far and originating from theoretic considerations, should include reducing of an overweight patient, mineral oil as a laxative, and a prolonged liquid diet. After the intra-abdominal pressure has been reduced in this manner, the patient should receive curare in sufficient dose to relax his abdominal muscles. Sitting in an upright position, he should then breathe an O_2 - CO_2 mixture through an anesthesia machine at a pressure of two or three atmospheres. The increased thoracic pressure could be made more effective by placing the patient in a swinging cradle, which reduces the intra-abdominal pressure subdiaphragmatically by abruptly lowering the abdomen and moving the intestines (centrifugally) away

from the diaphragm. Roentgen examination will show if this "active" medical treatment was successful. In some cases, adhesions between the hernia contents and hernial sac probably will prevent such a desired reduction of the prolapsed viscera.

SUMMARY

The definition, symptoms and diagnosis of subcostosternal diaphragmatic hernia are discussed. The common errors in the diagnosis of this condition are emphasized, and a case previously diagnosed as "heart disease" is reported. Indications for surgical treatment are presented. For cases without imperative reasons for surgery, the usually accepted medical measures are mentioned, and a more active medical régime is proposed for treatment of suitable patients who refuse surgical treatment.

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AGAMMAGLOBULINEMIA *

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AGAMMAGLOBULINEMIA is a syndrome first described by Bruton in 1952,¹ and later elaborated upon further by Bruton and Janeway² in the same year. This syndrome is featured by (a) a history of recurrent bacterial infections, (b) absence of acquired antibodies, (c) lack of isohemagglutinins, (d) extremely low to absent gamma globulin, although total serum proteins are within normal range, (e) failure of long-term antibiotic therapy to furnish protection, and (f) response to protective injections of gamma globulin.

CASE REPORT

This 30 year old white female was admitted to Ancker Hospital on November 21, 1953, with a diagnosis of meningitis.

Past History: Her first admission to this hospital was in December, 1950, when a diagnosis of pneumococcal meningitis was made, the smear and culture from cerebrospinal fluid being positive for *Diplococcus pneumoniae*. She was treated successfully with penicillin, Aureomycin and sulfadiazine, and was discharged from the hospital after 36 days of hospitalization. At that admission she gave a history of recurrent illnesses that dated back six years, to a time when she had developed sinus trouble while working in a defense plant. Ever since then she had had frequent attacks of headache, postnasal discharge and cough, and a gradual loss of weight.

She was admitted for the second time in January, 1951, for high fever, weakness, nausea and vomiting of two days' duration. Essential features at that time were a few râles in the right base, palpable axillary lymph nodes bilaterally, and enlarged spleen and liver. She stated that her spleen was first found to be enlarged on a routine physical examination in November, 1947, but no diagnosis was made after hospitalization for a week. The clinical diagnosis was Banti's syndrome and pneumonia. A chest film taken at this time is shown in figure 1. She was treated with penicillin, became afebrile and was discharged after 24 days.

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Her third admission was in May, 1951, for investigation of splenomegaly and anemia. The cause of the splenomegaly, anemia and lymphadenopathy was not determined. She was discharged after one month of hospitalization.

In November, 1951, the patient was examined in the clinic for polyarthrititis, sinusitis and possible hypersplenism. Multiple skin tests for allergy were done and all turned out to be negative.

The fourth admission was in December, 1951, with a diagnosis of recurrent pneumonia involving the mid left lung field. She was treated with Aureomycin and penicillin, and the response was excellent.

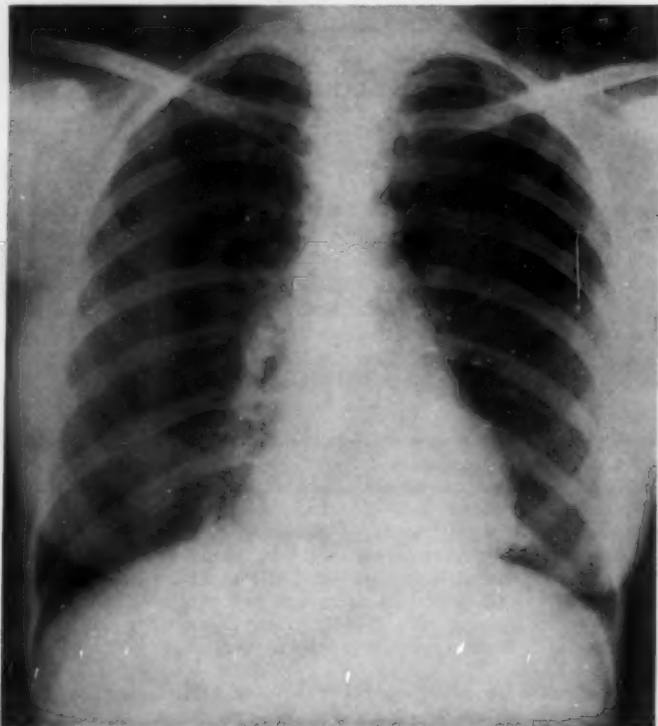


FIG. 1. Bronchopneumonia demonstrated on chest film taken February 13, 1951.

Her fifth admission was in April, 1952, for evaluation of her anemia. The anemia was attributed to hypersplenism, so the spleen was removed in May, 1952. So far as the anemia was concerned, the patient improved after splenectomy; however, no diagnosis was made as to the cause of splenomegaly. A section of the spleen demonstrating granulomata is shown in figure 2. A section of the liver biopsy with similar granulomata is shown in figure 3. At that time, a diagnosis of sarcoidosis was considered but was not established.

In October, 1952, the patient was admitted for the sixth time with a diagnosis of bronchopneumonia on the right side. She was treated with penicillin and Terramycin

and was discharged after 19 days of hospitalization. Ten days following her discharge she once again entered the hospital, and this time evidence of pneumonia was found in the left lower lobe. She was again treated with penicillin and was discharged after 18 days.

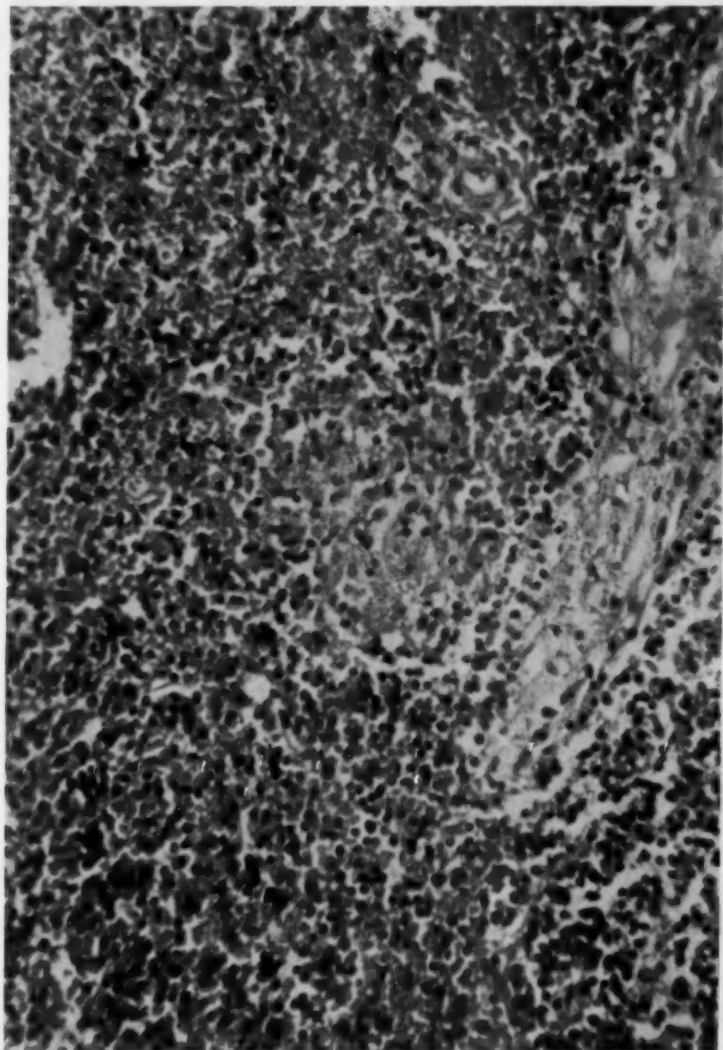


FIG. 2. Section of spleen, $\times 100$, from patient with agammaglobulinemia. Granulomata are demonstrated.

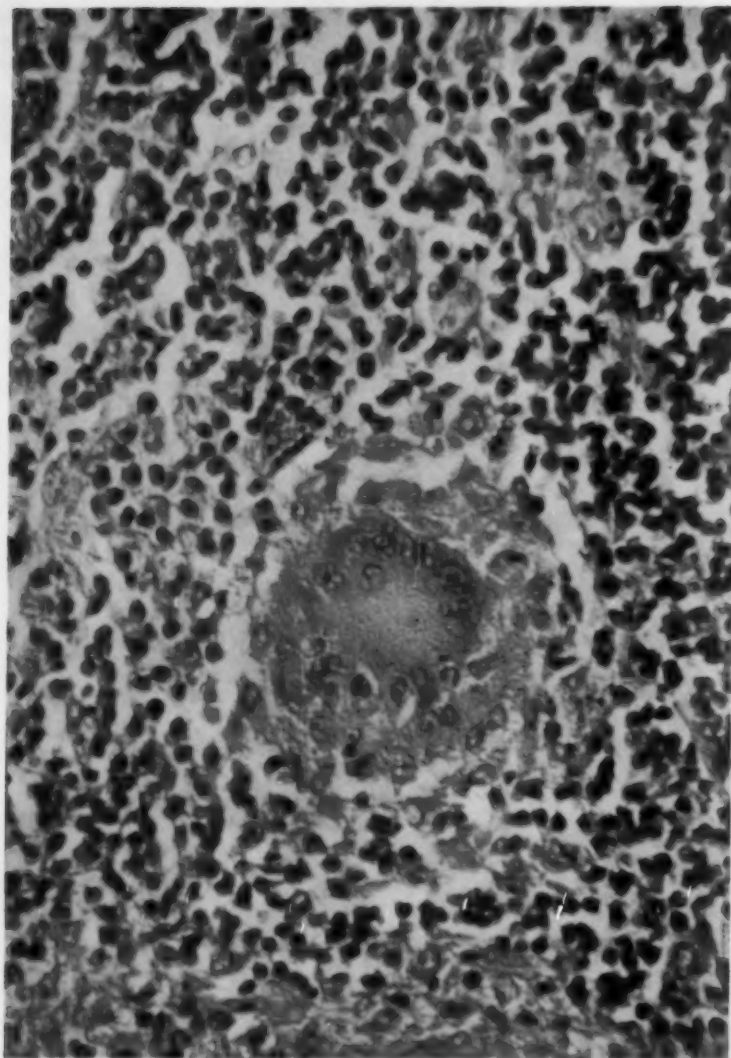


FIG. 3. Section of liver biopsy, $\times 300$, from patient with agammaglobulinemia. Granulomata are demonstrated.

The eighth admission to the hospital was in January, 1953, for a spinogram, which was essentially negative. She was discharged from the hospital but soon afterwards became febrile and so was again admitted to the hospital. At this time she developed a generalized rash, and a diagnosis of measles was entertained. Râles

were noted on both sides of the chest, and the diagnosis of recurrent pneumonia was considered. She was treated with penicillin and Aureomycin, and satisfactory clinical response followed. She was discharged after eight days of hospitalization. Figure 4 shows a chest x-ray film taken during this illness.

Her last admission was on November 21, 1953, for meningitis.

Family History: Her father and mother are living and fairly well. She has one brother and two sisters. One of the sisters suffers from infection rather frequently. Her brother is in the Army. She has one daughter, five years old, who is well.

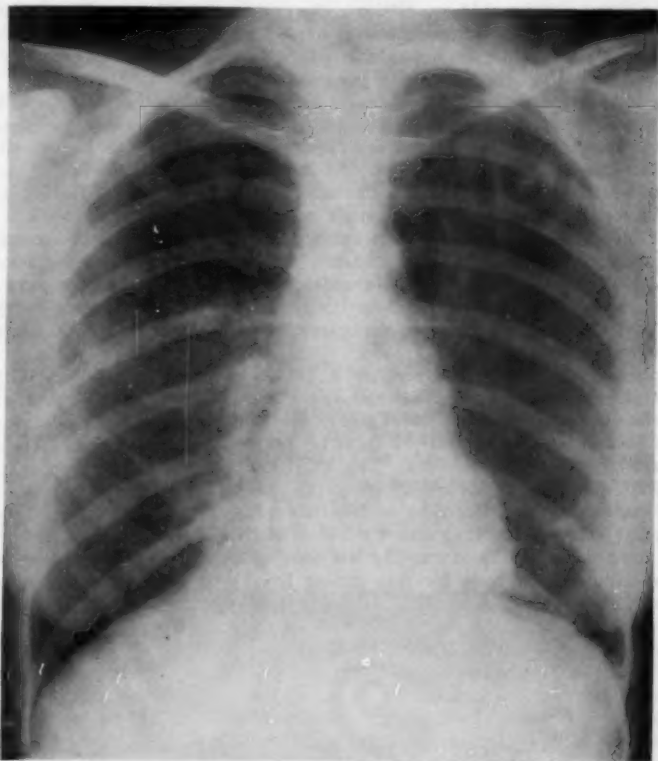


FIG. 4. Bronchopneumonia demonstrated on chest film on May 4, 1953.

Social History: The social history is not remarkable.

Physical Examination (on admission): The temperature was 101.0° F.; pulse, 110/minute, regular; blood pressure, 144/80 mm. of Hg. The patient was a well developed and well nourished 30 year old white female.

Positive findings were rigid neck, positive Kernig's sign, scattered râles in the left lower lobe and right middle lobe of the lung, and generalized lymphadenopathy. The clinical diagnosis was meningitis. The cerebrospinal fluid smear was positive for *D. pneumoniae*, and blood culture was reported to be positive for the same

organism. She was treated with aqueous penicillin, 400,000 units every four hours, sulfadiazine, 1.0 gm. every four hours, and Terramycin, 500 mg. every six hours for two weeks. She became afebrile after four days of therapy.

Laboratory Results: The patient had had numerous laboratory tests in an attempt to elucidate the etiology of her repeated bacterial infections. The compilation includes earlier studies made by private physicians,* as well as those made at the Ancker Hospital since her history was first taken in 1947.

The routine urinalyses have been normal. The blood Wassermann and Kahn tests have been negative. The hemoglobin determinations have been reported between the range of 8.3 to 13.5 gm./100 c.c., the present value being 12.9 gm./100 c.c. In May, 1951, the hemoglobin concentration was 8.3 gm./100 c.c. In 1952, just before the splenectomy was done, the hemoglobin was 9.4 gm./100 c.c. Erythrocyte counts have varied from 3,980,000 to 5,130,000 per cubic millimeter.

The leukocyte count on the most recent admission (November, 1953) was 68,487 per cubic millimeter, with a differential cell count of 95 per cent neutrophils and 5 per cent lymphocytes. The count fell rapidly during therapy to 10,200 cells per cubic millimeter in the next seven days. A similar granulocytic response to bacterial infections was noted on all other previous admissions for infections. During periods free of bacterial infections there had been a normal distribution of the various types of white blood cells. The eosinophils reached a value of 6 per cent recently but usually the count was much lower. Studies of the peripheral blood for immature cells had always been negative. In November, 1950, when sulfonamides were being given, the leukocyte count decreased to 1,500 cells per cubic millimeter but slowly rose to normal values. Just before the splenectomy the count was 2,700 leukocytes per cubic millimeter.

A platelet count made on December 2, 1953, was 611,000 per cubic millimeter, and the majority of the other determinations were normal. The lowest platelet count before the splenectomy was 78,000 per cubic millimeter. The reticulocyte count over the last three years has varied from 1.6 per cent to 2.4 per cent. The MCV has been 80, 88 and 98 cu. microns. The MCH has been 23, 24 and 28 micrograms. The MCHC has been 29, 27 and 29 per cent. The MCD was recorded as 7.0, 7.4 and 7.2 microns. A bleeding time on November 3, 1952, was 1 minute 10 seconds. The capillary coagulation time was 4 minutes, and the Lee-White coagulation time was 12 minutes. A red blood fragility test done on December 17, 1951, was normal.

The sedimentation rates for this patient have been extremely interesting and significant. During the years 1947 to the present date 21 sedimentation rate determinations were made. Even though most of these were made during periods of acute infection, only one high value of 37 mm./hr. was recorded, on February 1, 1951; all other determinations were 16 mm./hr. or lower.

Most of the chemical studies carried out on this patient were essentially normal. The blood urea nitrogen determinations ranged from 8.4 to 14 mg. per cent. The bicarbonate level of the blood varied from 25.7 to 31.1 mEq./L. The bilirubin determination showed zero direct bilirubin and 0.26 and 0.56 mg. per cent total bilirubin on two determinations. The thymol turbidity determination was 1.3 units. The quantitative fecal determinations of urobilinogen were 40 Ehrlich units per 100 gm. of feces on December 3, 1953, and 160 Ehrlich units/100 gm. of feces in December, 1951. The quantitative urine urobilinogen determination on December 1, 1953, was 0.3 Ehrlich units/2 hrs. The phenolsulfonphthalein excretion test on December 29, 1953, showed 40 per cent excretion in 15 minutes, 18 per cent excretion in 30 minutes, and 6 per cent additional excretion by the end of the hour, making a total of 64 per cent excretion in one hour. On December 1, 1953, the value for the alkaline phosphatase was 6.1 units. The plasma chloride values, except for the post-splenectomy period, have been in a normal range of from 98.1 to 104.8 mEq./L.

* Supplied through the kindness of Dr. D. R. Gillespie, Earl Clinic, St. Paul, Minnesota.

A Congo red test done on June 4, 1951, showed 70 per cent retention in the blood. This same value was obtained when the test was repeated on January 11, 1954. A cephalin-cholesterol flocculation test on June 8, 1951, was negative at 24 hours and 1 plus at 48 hours.

The most interesting laboratory study is that of the serum proteins. Four routine laboratory determinations were made. The first two in 1951 were more nearly normal, but the determinations made in December, 1953, showed a great change. These determinations were as follows:

Date	Total Serum Proteins	Albumin	Globulin
Feb. 5, 1951	5.80 gm.%	4.64 gm.%	1.16 gm.%
Dec. 15, 1951	6.20	4.56	1.64
Dec. 1, 1953	5.55	4.76	0.79
Dec. 5, 1953	5.50	4.56	0.94

As a result of this finding of reduced globulin, we obtained electrophoretic studies of this patient's serum proteins.* The electrophoretic tracing is shown in figure 5. The values obtained for the fractions of the serum proteins are:

Albumin	3.7 gm.
α_1 Globulin	0.6
α_2 Globulin	0.6
β Globulin	0.7
γ Globulin	0.0

The total proteins for this determination were 5.6 gm. The interpretation of this tracing was that it was typical of agammaglobulinemia.

The tests for agglutinins in the blood have been all negative. On September 18, 1947, the agglutinins for *Brucella abortus* were absent. On December 14, 1951, and again on December 1, 1953, a whole battery of agglutination studies were negative. These two studies included Typhoid O, Typhoid H, Paratyphoid A, Paratyphoid B, *Br. abortus* and Proteus OX 19. Heterophil antibody and cold agglutinins were negative. The patient's blood type was reported as O, Rh positive.

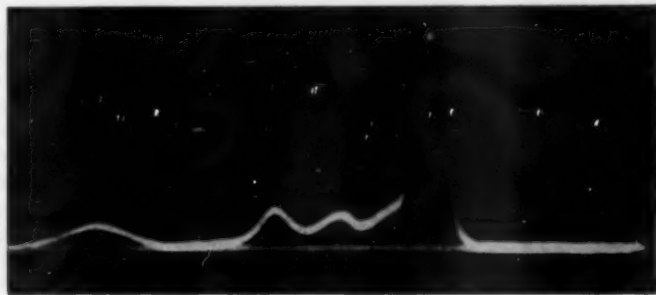


FIG. 5. Electrophoretic study done on serum of patient on December 8, 1953. Agammaglobulinemia is demonstrated. This examination was done with a portable model of the American Instrument Company. A Veronal buffer with pH of 8.6 was used at 10 milliamperes. Two hours were allowed for separation.

* The electrophoretic examination was done by Dr. H. Zinneman, Minneapolis, Minnesota.

Seven Mantoux tests have been negative. Skin tests for histoplasmosis, blastomycosis and coccidioidomycosis were negative. The sickling trait was absent, and the Coombs' test was negative.

Blood cultures taken on November 24, 1952, February 17, 1953, and November 21, 1953, had a growth of organism identified as *D. pneumoniae*. This same bacterial organism was cultured from the spinal fluid on November 17, 1950, February 8, 1953, and November 21, 1953. No organisms were cultured from the excised spleen.

REVIEW OF THE LITERATURE

The first report in the literature was that of Bruton in 1952.¹ He reported three cases, all males, whose average age was nine years. The common illnesses in these children consisted of pyoderma, purulent conjunctivitis, otitis media, purulent sinusitis, pneumonia, meningitis, acute arthritis and septicemia. The organisms isolated in these cases were pneumococcus, *Staphylococcus aureus*, *Hemophilus influenzae* and meningococcus. The infections usually responded quickly to antibiotics and sulfonamide therapy, but recurred at frequent intervals. The children were all observed to be normal as to their state of nutrition and physical development.

The first patient reported was a nine year old boy who had been followed by Bruton over a four year period because of 19 different episodes of sepsis, along with recurrent pneumonitis, otitis media and mumps. Blood cultures were positive in 10 different instances for eight different types of pneumococcus. Prophylactic sulfadiazine was ineffective in preventing recurrent infections. Autogenous pneumococcal vaccine, as well as commercial pneumococcal polysaccharide vaccine, was administered without any manifestation of antibody formation. A Schick test remained positive in spite of additional diphtheria toxoid injections. The administration of typhoid was not followed by the appearance of antibodies. Similarly, no complement-fixing antibodies were demonstrated in spite of recurrent attacks of mumps. Electrophoretic studies of the patient's sera revealed a complete absence of gamma globulin. The total proteins were within normal range. This boy was treated with human gamma globulin intramuscularly at monthly intervals, with remarkable results.

The other two boys had similar episodes of infection, but recurrent pyoderma, sinusitis, pneumonia and pyogenic arthritis appeared more conspicuous. One patient had *H. influenzae* meningitis. Specific antibodies were not demonstrated in the serum in spite of a series of injections of diphtheria, pertussis and tetanus toxoid, pneumococcal polysaccharide and influenza A and B vaccines. The total protein, albumin and globulin, as measured by routine procedures, appeared normal. Gamma globulin was found to be absent on electrophoresis, although minute amounts could be detected by immunochemical methods. Electrophoretic studies of the sera of the siblings, parents and one set of grandparents of the latter two boys revealed normal gamma globulin concentrations.

In August, 1953, Zinneman² reported the case of a 29 year old male who had a history of recurrent lower pulmonary infections. Electrophoretic studies of this patient's sera revealed a typical pattern of agammaglobulinemia.

In a recent article Janeway et al.³ report that they have collected a group of nine cases, six observed personally in his clinic and three reported to him by other investigators. These patients were all children, and it is Janeway's opinion that further investigation must be carried out to determine whether the defect of the

antibody-forming tissues is congenital or acquired. Especially significant is the opinion that this condition is possibly a sex-linked inheritance, in that these cases have all been males. Although all of Janeway's patients failed to show gamma globulin on electrophoretic analyses, immunochemical studies indicated that very small amounts (less than 30 mg. per cent) of gamma globulin may be present in certain cases. The histologic sections of one autopsied case, when studied by histo-immunochemical techniques, revealed a paucity of gamma globulins in their usual distribution in the connective tissues. Lymphoid tissue was noted as being markedly diminished. These contributions of Janeway are very important in their further clarification of some of the defective mechanisms underlying this condition.

Schick and Greenbaum⁵ in 1945, reported a case of low serum gamma globulin associated with low total serum proteins. The patient was edematous but showed no predisposition to bacterial infections; however, no electrophoretic or immunochemical studies were done. These authors explained the presence of antibodies in gamma globulin and cellular immunity based on the potential ability of the reticuloendothelial system to reproduce antibodies quickly in the absence of gamma globulin.

Gitlin² in 1952 studied and reported a few cases resembling the one reported by Schick and Greenbaum. These patients, however, showed a level of 100 to 200 mg. of gamma globulin per 100 c.c. of blood on immunochemical analysis. This finding led Gitlin to believe that a level of 100 to 150 mg. of gamma globulin per 100 c.c. of blood may prevent infection.

In 1935 McQuarrie et al.² reported the case of an edematous child who died at the age of three and one-half years following an ear infection complicated by mastoiditis and sepsis. At autopsy, atrophy of the hepatic cords was found to be present, most prominently in the mid and peripheral zone of the liver lobule. No evidence of fibrosis or inflammation was noted. These authors postulated that the injured liver was unable to replace the loss of protein and gamma globulin.

Krebs⁶ emphasized an important relationship in his case. This was one in which depression of gamma globulin was noted in association with hypoproteinemia due to malnutrition. The patient was treated with proper diet and gradually improved. Krebs concluded that the production of gamma globulin is dependent to some extent upon the diet.

DISCUSSION

This is the first case of a female with agammaglobulinemia reported in the literature. All of the characteristics of this syndrome as elaborated by Bruton and Janeway were present in our case. Furthermore, in contrast to the previously reported cases, in which the patients were children, our patient was an adult of 30 years, the mother of one normally developed child. It is important to note that the onset of recurrent bacterial infections had begun about four years earlier, the patient having enjoyed relatively good health up to that time, with only the usual childhood diseases. This would certainly indicate that this patient has to be considered as representing an acquired form of agammaglobulinemia. In addition, she presented a complicating feature of generalized peripheral lymphadenopathy, hepatomegaly and splenomegaly. The splenomegaly was complicated by an acquired hemolytic anemia, which was promptly resolved by splenectomy. The presence of numerous nonspecific granulomata demonstrated on histologic sections

of the spleen and biopsied axillary lymph node would implicate a disease process involving the reticuloendothelial system. However, to date there has been no explanation of this granulomatous process.

In regard to Janeway's suggestions of a possible sex-linked factor in these cases, consideration of our patient would tend to invalidate this for all cases. However, it might also be stated that the previously reported cases, all young children of the male sex, might represent a congenital type due to a sex-linked factor. Our case, an adult female, most likely represents a case of an acquired form. Thus one would expect that the congenital type would be sex-linked, and therefore confined to young males, whereas the acquired form could appear in either males or females. However, the delineation of this problem must await many more reports of such cases.

Felton has postulated that "immunological paralysis" can be produced in man and in mice by an appropriate dose of antigenic polysaccharide, thereby causing an acquired dysfunction of the reticuloendothelial system and subsequent lack of production of antibodies. However, one might expect that with the cessation of administration of the antigenic polysaccharide and the supplying of enough antibodies, the reticuloendothelial cells might be freed from the blocking effect produced by the antigen and thereby produce antibodies. In other words, one could expect such cases to become normal after a few injections of gamma globulin. However, Bruton's cases showed the definite need for repeated injection of gamma globulin at monthly intervals. Bruton interpreted this fact as evidence against its being an acquired condition, and speculated whether this condition, like afibrinogenemia, is a congenital protein abnormality, or reflects defective function of the reticuloendothelial system. It is not possible to solve the problem at this time, and there is need for further investigation of this syndrome.

In our case, it may be possible that some infection resulted in granuloma formation, thereby damaging the reticuloendothelial system and producing agammaglobulinemia. Still another possibility is that the lymphadenopathy and splenohepatomegaly represent compensatory hyperplasia due to agammaglobulinemia, and that the granuloma formation is unrelated to this.

Phenylthiourea taste test was performed in this case and the patient was able to taste the substance. This was done in the hope that this may be of some interest to those concerned with genetics.

SUMMARY

A case is presented of an adult female with repeated infections, a granulomatous process involving the reticuloendothelial system, and agammaglobulinemia.

ACKNOWLEDGMENT

We are grateful to Dr. E. B. Flink and to Dr. H. R. Zinneman, Veterans Administration Hospital, Minneapolis, for the advice and assistance given to us in the preparation of this paper.

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A CASE OF PERIARTERITIS NODOSA WITH L.E. CELLS; APPARENT COMPLETE REMISSION WITH CORTISONE THERAPY *

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Seldom is the diagnosis of periarteritis nodosa made in time to do much in the way of therapy. It is therefore a dread disease. It has been noted by DuBois¹ that it is sometimes possible to alter the statistical incidence of rare diseases by training a hospital staff to become conscious of a disease syndrome and on the alert to diagnose the ailment early when, presumably, treatment may be effective. He cites the case of disseminated lupus erythematosus. Considered a rarity, the diagnosis was made 11 times in the Los Angeles County General Hospital in the years 1948 and 1949. However, in the following two years, after the hospital staff became alert to the existence of systemic lupus, and checked obscure but possible cases by the use of the blood test devised by Hargraves² for lupus erythematosus cells (the so-called L.E. cells), a total of 44 cases was diagnosed. This put the disease above Hodgkin's and pernicious anemia in relapse in statistical frequency. Neither of these diseases is generally considered rare in the hospital population.

The following account of a case of periarteritis (also a collagen disease) is reported for two reasons:

First, to stimulate increased alertness to the syndrome. This case presented a textbook array of the classic symptoms of periarteritis nodosa, but the diagnosis was missed by three consecutive doctors because the symptoms, though typical, were vague and mild and "out of mind." Presumably it might have progressed to a fatal conclusion with only a terminal diagnosis had not the patient been lucky enough to develop a high fever, a distress signal too lurid for any doctor to overlook.

Second, because of the remarkable improvement evidenced immediately after cortisone therapy was started. Six months later the patient was working and appeared well clinically. A repeat tissue biopsy showed no evidence of periarteritis nodosa (figures 1-3).

* Received for publication February 6, 1954.

CASE REPORT

A 56 year old white married woman considered herself well until December, 1952, when she suffered mild leg muscle distress and was tired out of proportion to her activity. She also had for a few days a fine generalized rash that itched . . . "Maybe hives from something I ate at holiday time." Because these symptoms came at the time of a winter epidemic of "flu" she thought they might be "flu," but did not think she had any fever. On January 3, 1953, she first consulted a doctor (the author), who could offer no explanation except a possible anemia not confirmed by

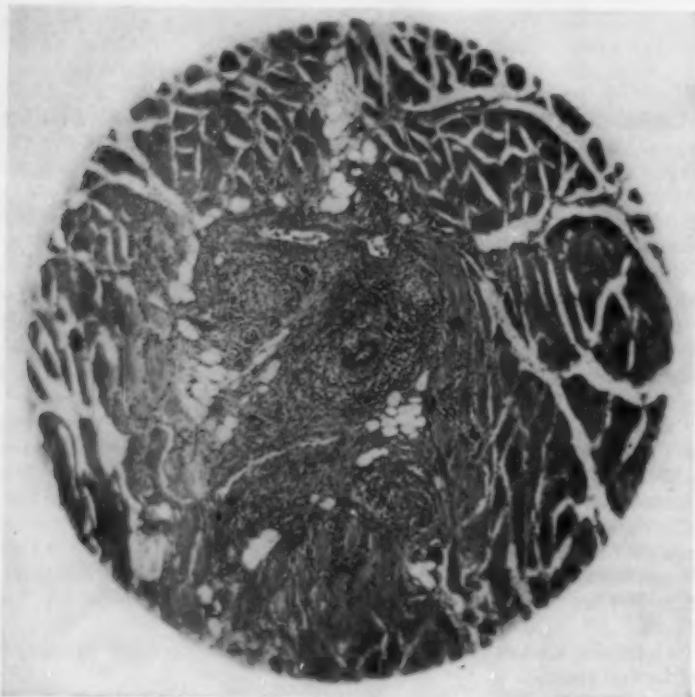


FIG. 1. Low power magnification of a typical lesion of periarteritis nodosa, showing infiltration around a small artery with round and plasma cells and a few scattered eosinophils.

the normal blood count. In the next six weeks she consulted two other physicians—an internist and a surgeon—neither of whom found anything wrong. On March 2 she again presented herself with the vague story of excessive fatigue, weakness and mild discomfort in the calves of her legs. She denied any more helpful symptoms, and stated that she was sure she had had no fever . . . she was "just tired and weak."

Although she did not look particularly ill, she had at that moment a fever of 102° F. Her blood pressure, which had been 140/90 mm. of Hg when she was seen six months previously, was now 90/60 mm. of Hg, a startling drop. She was hospitalized for diagnostic study.

For the next 10 days an exhaustive search was made for a cause for the fever,

which spiked daily from 100° to 102° F. In spite of the high and persistent fever she did not appear as ill as such a patient usually does. Of an uncomplaining temperament, she could be coaxed into describing no distress but "tiredness" and mild discomfort in the left calf. Previous history was not helpful. She had experienced a period of excessive fatigue and some backache, diagnosed as "an intervertebral disc," some two or three years earlier. About a year earlier she had been treated for overweight and a blood pressure that was 160 to 180 over 90 and which dropped to

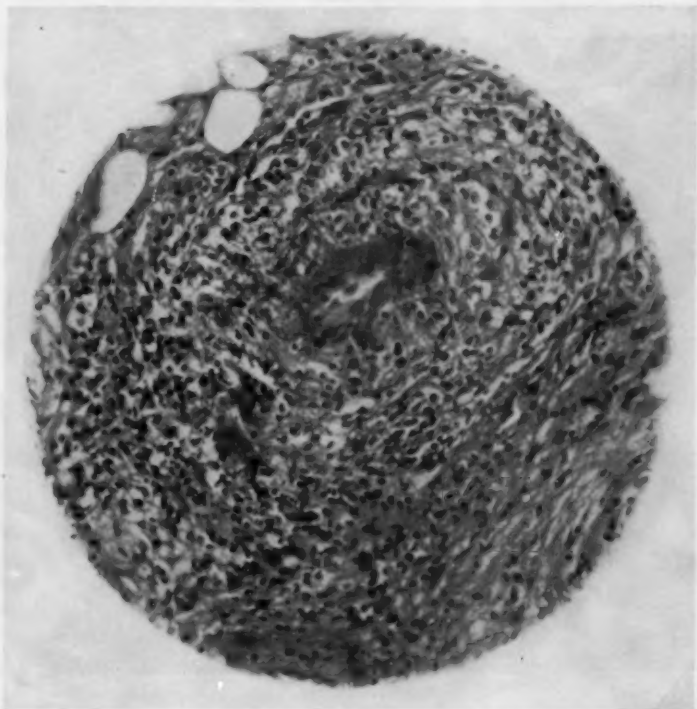


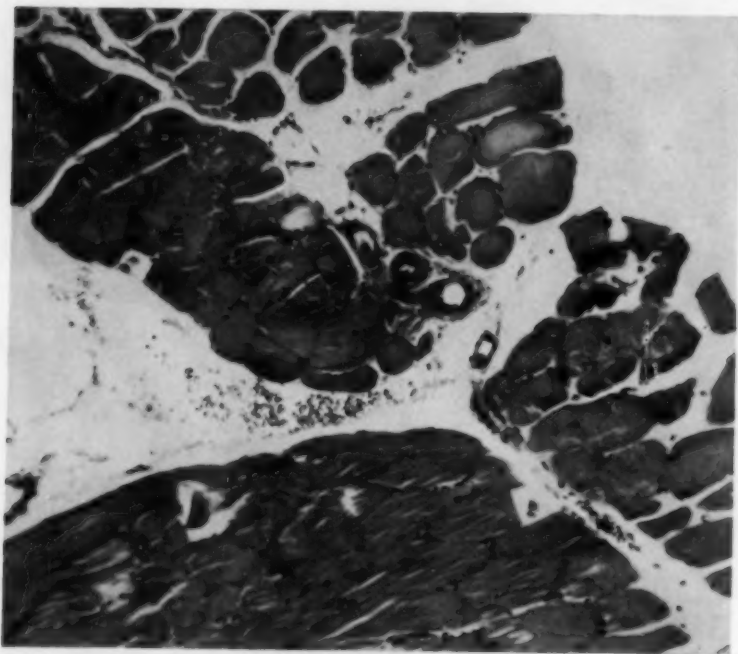
FIG. 2. A higher power magnification of the same affected small artery, showing great damage to the arteriole with considerable necrosis of the wall, with remnants of wall visible at the left. There is a heavy infiltration of round cells, plasma and eosinophils, with a considerable developing periarterial fibrosis.

140/84-90 after she lost 25 pounds over a five month period on a high protein, low fat and carbohydrate diet. She had taken small doses of a preparation of veratrum in the spring of 1952.

That summer and fall she had been busy and well. She denied using raw milk, and disliked and avoided pork. She had had contact with a changing group of war veterans returned from various areas where malaria existed, but had suffered no symptoms suggestive of malaria. System review gave no leads.

Physical examination revealed a well developed and well nourished woman of 56 weighing 132 pounds, an excess of 10 to 12 pounds over her ideal weight. She

did not appear ill. Her temperature was 102° F. by mouth. The skin was clear, and the mucous membranes were of good color. The graying hair was tinted. She wore glasses and dentures. Eyes, ears and nose were not remarkable. There were no palpable glands anywhere. Breasts, chest, heart and lungs were all normal. Blood pressure was 94/56 mm. of Hg. The abdomen was negative and the spleen could not be palpated. The pelvis was normal for a postmenopausal multipara. The rectum was not remarkable except for several small external hemorrhoidal tags. The reflexes were in order. There was minimal tenderness on deep pressure over



A

FIG. 3. Sections (A, B and C) from muscle biopsies, after six months of treatment, from the same area as shown in figures 1 and 2. Blood vessels are of normal caliber and show no evidence of inflammatory reaction in the walls or in surrounding striated muscle.

the left calf muscle. There was no heat or redness of this area. The only signs to serve as leads were the fever, the known drop in blood pressure, and the extremely slight muscle tenderness in the left leg. She always felt "fine, only tired."

All of the routine laboratory work to track down the reason for fever was done, and much of it was repeated, all with negative results. Because of the patient's exasperatingly vague symptoms, her complaint of weakness and the striking drop in known blood pressure, a Thorn test for cortico-adrenal function was done and gave completely normal results. The blood work was not helpful. White blood counts ran from 12,000 to 14,900, polymorphonuclear cells ranging from 68 to 80 per cent, monocytes from 5 to 7 per cent. In one early differential there was an increase in

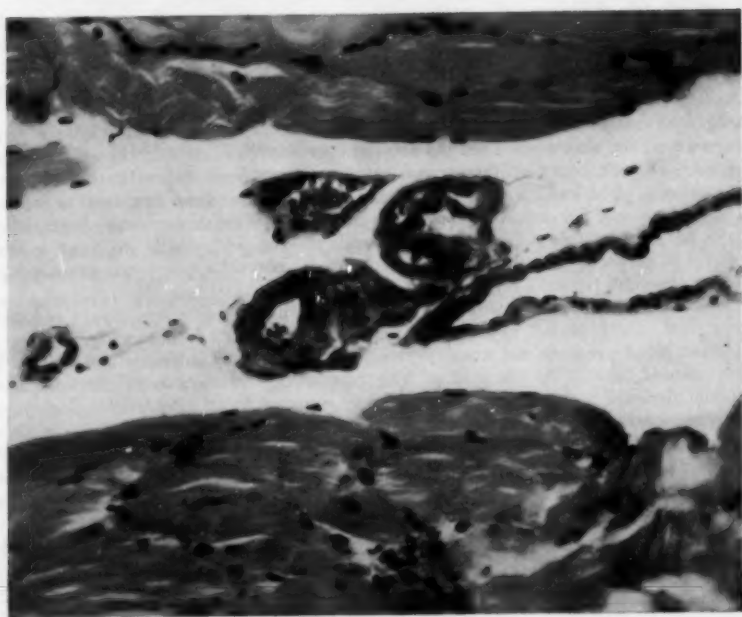
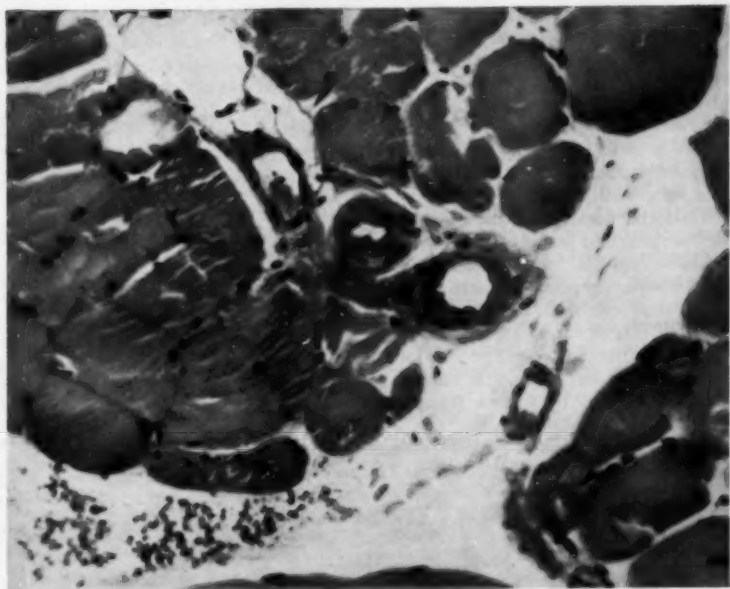


FIG. 3 B (above) and C (below).

the eosinophils not present in subsequent counts. Her blood sedimentation rate was 80 mm. by the Westergren method. The blood Wassermann test was negative. Two blood cultures were negative. Agglutinations for undulant fever, typhoid, and paratyphoid fever A and B were negative. Repeated smears for malaria were all negative. The chest x-ray was normal. Sputum smear and culture were negative. An intravenous pyelogram was normal. Two catheterized urine cultures failed to show any growth of pathogens. A complete upper and lower gastrointestinal series was negative. Stool examination showed no amebae or parasites, and a stool culture showed no growth of pathogens.

While the question of muscle biopsy was being discussed in the light of the negligible symptoms and the dearth of leads, the physician examining the blood smears for malaria noted a rise in eosinophils and the biopsy was done. A sizable chunk of gastrocnemius muscle was taken from the area of the left calf where the tenderness had been most evident. Reported as follows, it established the diagnosis:

"Three fragments of gastrocnemius muscle, each 1 cm. in maximum diameter, on multiple section show well retained musculature but many small arteries as well as a few medium-sized ones are surrounded by dense inflammatory reaction predominantly lymphocytic with a few scattered eosinophils. One shows some hyalin degeneration of the wall.

"Diagnosis: Lesions of periarteritis nodosa of striated muscle."

With the diagnosis at last established by the positive biopsy findings, a search was made for lupus erythematosus cells, the so-called L.E. cells of Hargraves. They were found in the buffy coat of blood in a sedimentation rate tube. This is an unusual finding, but it serves as a further confirmation of the diagnosis.

TREATMENT

Immediately following the pathologic report, the patient, whose fever was a daily 102° F., was started on cortisone by mouth in divided doses at six hour intervals, a daily total of 300 mg. The fever subsided dramatically within 24 hours and remained normal. After three or four days the dose of cortisone was slowly reduced at the rate of 12.5 mg. at a time, until after 10 days of therapy it was slightly under 150 mg. At that point her temperature rose one degree. The cortisone was promptly increased and she was discharged on 150 mg. per day in divided doses at six hour intervals. She felt better on the same dose taken at six hour intervals than at eight hour intervals. She had been taught how to prepare a low-sodium diet, how to record her weight, to test her urine for sugar, to record her fluid intake and output, and to take her temperature. Being a meticulously careful individual, she kept a fine daily record of these essentials for months. She also took a potassium preparation (Lilly's potassium triplex) regularly.

Her improvement was steady and gratifying. The cortisone was slowly reduced over a four month period to 50 mg. a day. Blood levels of sodium, calcium and potassium, blood pressure and urine were checked at monthly intervals and remained within normal limits. At the end of four months of treatment with cortisone she felt better than she had in years and voluntarily returned to an afternoon bookkeeping job at her husband's place of business. In mid-August she went on a fortnight's vacation trip, driving to the Canadian Rockies. She had a fine vacation in spite of the high altitude and the difficulty in managing her low sodium diet in hotels. She did gain five pounds, which was probably partly fluid but which she has not been able so far to lose.

Within two months of the start of cortisone therapy, which was of rather high dosage, she developed the classic moon-face, which neither she nor her husband disliked, as she had naturally a rather long, lean, British type of feature and it was not displeasing. She has noted that her legs and ankles, always inclined to be heavy,

are smartly slim for the first time in her life. She has not herself commented on the typical fat pads about the neck, but she noted less fat on the hips and more on the abdomen.

At the end of six months of cortisone therapy it seemed time to appraise the situation and plot future therapy. The patient cooperated by allowing another biopsy of the left calf muscle. The tissue was taken next to the scar of the first biopsy, in a region that might reasonably be expected to show blood vessel pathology. The tissue was studied by the same pathologist as was the blood taken for a check on the blood chemistry and on the existence of L.E. cells. The pathologic reports follow:

"Biopsy of left gastrocnemius: The specimen is composed of a piece of muscle measuring 3 by 1.2 by .8 cm. which is cut into several sections and all of the tissue embedded. The patient has previously been biopsied and a diagnosis of periarthritis nodosa made.

"Microscopic section of the muscle includes numerous vessels, including arterioles and small arteries. At only one place is there any evidence of residual inflammation and this is merely a small cuff of lymphocytes around one of the smaller vessels. The changes of periarthritis nodosa are not seen in either active or subsiding phases. This tissue will be cut deeper and further reported."

Second report: "This muscle is restudied and additional sections are cut deeper in the material. The recut demonstrates small and medium arteries as well as other vessels and in none of these is there evidence of inflammatory change of any type.

"Diagnosis: Essentially normal striated muscle."

Since the presence of L.E. cells prior to cortisone therapy helped clinch the diagnosis, a repeat test for them is of interest and follows:

"The smears are prepared by the Hargraves technic of expressing clotted blood through a 40 mesh screen centrifuging and examining the buffy coats. In this manner, several hundred cells, at least, are observed. In the present material there is no evidence of specific lupus erythematosus inclusions nor are any of the hematoxylin bodies encountered.

"Diagnosis: No. L.E. cells found."

The finding of L.E. cells in the blood of a patient with proved periarthritis nodosa is not only of help diagnostically but also is of considerable academic interest. It is also interesting that blood vessels showed no fibrosis or scarring or even evidence of healing. They were simply normal blood vessels. Since they came from the same area as the initial diagnostic tissue, they should give a fair indication of the present condition of arterioles and arteries in the location known to have contained injured vessels. Unfortunately, we have no good way of appraising arteries elsewhere. The patient's urinalysis remains free of any evidence of kidney involvement, a further evidence of possible "cure," since many of these patients die of extensive kidney artery damage and the resulting hypertension.

ADDENDUM

In mid-February, 1954, (approximately one year after beginning cortisone therapy,) the patient had a sudden onset of fever of 103° F., general malaise, chest pain and cough. She was hospitalized and found to have a lobar pneumonia involving the right middle and lower lobes. She was given large doses of Achromycin and at the end of 10 days was well, with a complete resolution of the pneumonia as demonstrated by x-ray. She was discharged from the hospital on a maintenance dose of 40 mg. of cortisone per day. She remained well, with no evidence of untoward effect from the pneumonia.

DISCUSSION

When the cessation of therapy will seem wise is still to be discovered. It takes courage to change a course that seems to work well, and it could reasonably require many months, perhaps years, to heal completely such extensive blood vessel damage as this patient showed. The present plan is to try reducing the cortisone to 35 mg. at the end of a year of treatment, and possibly to discontinue it at the end of 18 months. Perhaps by then more information will be available.

Whether this biopsy report of normal blood vessels, loss of L.E. cells, and the disappearance of symptoms mean a spontaneous remission, a therapeutically induced remission or even a "cure" is anybody's guess. Occasional reports^{3, 4, 5, 6, 7} of remissions and of apparent healing after the use of ACTH and cortisone are beginning to appear in the literature. Surely these substances offer the best therapy yet available. And, just as surely, if we as clinicians were more alert to the early manifestations of periarteritis nodosa, the disease might be found to be neither so rare nor so frequently fatal. The routine use of the L.E. cell test on the patient with the vague weakness and mild symptoms seen in that hazy no-man's land where the neurotic complainer and the early collagen disease victim dwell might lead us to a new attitude toward periarteritis nodosa.

SUMMARY

A 56 year old white married woman, hospitalized for high, unexplained fever, is diagnosed by finding L.E. cells in the blood and by leg muscle biopsy as having periarteritis nodosa. Dramatic improvement follows treatment with relatively large doses of cortisone. A second muscle biopsy at the end of six months of treatment shows normal muscle, suggesting the possibility that prolonged large doses of cortisone can facilitate the remission or healing of periarteritis nodosa. L.E. cells disappeared from the blood. The difficulty of early diagnosis is emphasized.

Grateful acknowledgment is made of the assistance of Mr. Jack R. Newby, Dept. of Medical Illustration, University of Washington.

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EDITORIAL

BCG VACCINATION

VACCINATION against tuberculosis with BCG has been a debated subject for many years. The majority of the large number of investigators who have expressed themselves on the subject are favorable and many are highly enthusiastic toward its use. A minority, influential in professional standing, have opposed it, or at least urged caution and delay until further study furnishes unequivocal evidence of both its safety and value.

Part of the argument centers on the fact that BCG vaccine consists of live bacteria. The microorganism employed is an avirulent mutant from an originally virulent strain of tubercle bacillus, and in any long-range consideration the possibility of reversion to a virulent status cannot be ignored.

All available reliable evidence indicates, however, that in the thirty years during which BCG has been employed in the vaccination of human beings, no significant change in the direction of increased virulence has taken place. It is now generally conceded that the Lübeck disaster was due to a gross mistake, in which a recently isolated virulent strain of bacillus was used for the vaccine; and the claims of Petroff, which were widely discussed some twenty years ago, have not been confirmed, even though the studies themselves furnished much useful information on bacterial dissociation. An exhaustive analysis of the contradictory reports in the early period of BCG vaccination led a careful student of the problem, K. N. Irvine¹ to the conclusion that since 1930 BCG had been incapable of producing progressive tuberculosis in laboratory animals, that it had never proved virulent for man, that the very few cases truly subject to suspicion occurred before 1930 and that since that date no acceptable evidence had been put forward which puts in question the safety of BCG for human vaccination. While occasional claims of untoward results have been made since Irvine's statement, they have failed to be substantiated, and the general consensus today is in agreement with the statement of Irvine years ago.

It is indeed true that some mutation of BCG strains does occur. The three strains in use in this country, which will be discussed later, vary in colonial growth and character (Vandiviere, Willis, Melvin and Gentry²). No one of them, however, in spite of some variation in the tissue reaction and allergic sensitivity it produces, has ever produced progressive disease in animals or man.

The principal objections raised to BCG today are (1) that it destroys the value of the tuberculin test as an index of community infection, since it

¹ Irvine, K. N.: BCG vaccination in theory and practice, 1949, Blackwell Scientific Publications, Oxford, England.

² Vandiviere, H. M., Willis, H. S., Melvin, Irene, and Gentry, W. H.: New techniques in the comparative study of BCG and R₁, Trans. 49th Annual Meeting, Nat. Tuberc. Assn., 173-176, 1953.

converts its recipients to the tuberculin-positive state, and (2) that it alters the allergic status of the human body so that on subsequent spontaneous infection the so-called reinfection type of the disease, rather than the supposedly more innocuous primary type, occurs. These views have been expressed repeatedly and forcefully by Myers³ and Levine.⁴ Space is not available here to discuss them in the detail required for adequate presentation. In brief, it may be stated simply, however, that there is wide agreement that these possible disadvantages are outweighed by substantial advantages.

Although, as indicated, it is almost universally conceded that BCG vaccination is safe, there is not perfect accord as to its effectiveness in the prevention of tuberculosis. Here, too, however, the weight of published evidence is in favor of the proponents of the procedure. The original studies made in France and in areas of French professional influence, fell into some disfavor because they were not well controlled statistically. More recent studies, however, now so numerous that they need not be cited in detail, indicate that in any large series of vaccinated subjects and controls followed over a period of years cases of tuberculosis and deaths from the disease are four to seven times as numerous in unvaccinated controls as in vaccinated subjects. Once again it should be stated that exception is occasionally taken to the validity of the figures, but it must be conceded that majority opinion supports them.

At this point it might be well to review briefly the origins and history of BCG vaccination. The vaccine was developed in France in the early part of the twentieth century. Its use was based on studies made by A. Calmette and C. Guérin (hence the name BCG, bacillus of Calmette and Guérin) which were initiated as early as 1906. The BCG organism, an originally bovine strain of the tubercle bacillus, became nonvirulent in the course of prolonged cultivation on media containing bile. It was first tried on man in the early 1920's after lengthy studies on its safety and efficacy in laboratory animals, including primates. Following early favorable reports, its use was extended to French colonies and various parts of Europe and Latin-America. A remarkable development of the procedure took place in the Scandinavian countries, leading to an advocacy of the procedure not surpassed even in France. The Scandinavian program has had a profound influence on the development of the present world-wide campaign of the World Health Organization, in which at least twenty million persons have been vaccinated.

In England, Canada and the United States the method has been used much less extensively than in continental Europe and South America, in spite of the fact that several of the most widely quoted studies testifying to the efficacy of the vaccine have been carried out in Canada and the United States. Possibly the conservative attitude in these countries stems partly

³ Myers, J. A.: BCG vaccination, *Am. Rev. Tuberc.* 57: 107-109, 1948.

⁴ Levine, M. I.: Deficiencies in our knowledge of BCG vaccine, *Dis. of Chest* 21: 513-520, 1952.

from the fact that the antituberculosis campaign has proceeded in a not ungratifying manner without a vaccination program. It is noteworthy, however, that BCG vaccination is now increasingly practiced in these countries, and that under governmental direction its use is presently authorized on a voluntary basis in the state-operated tuberculosis clinics in Great Britain.

In the light of multiplying reports and increasing interest in the vaccine it is inevitable that responsible organizations have felt compelled to take a stand on BCG vaccination. A statement of conservative character, which has met with wide approval, was put forth several years ago by the American Trudeau Society, Medical Section of the National Tuberculosis Association.⁵ The document states in its opening paragraph that BCG vaccine prepared under acceptable conditions and administered by approved technics to persons negative to tuberculin, can be considered harmless. It goes on to say that the degree of protection afforded is by no means complete and the duration of the relative immunity produced is not permanent or even predictable. It emphasizes the need for further research on those points. It points out, however, that on the basis of studies reported in the literature an appreciable reduction in the incidence of clinical tuberculosis may be anticipated when certain groups of people who are likely to develop tuberculosis because of unusual exposure, inferior resistance, or both, are vaccinated. The statement lists those groups in some detail.

Statements of similar import have been made by other organizations, notably the U. S. Public Health Service.⁶ All of them stress the imperfections in our present knowledge of BCG vaccination and recommend continued controlled investigation of the procedure. A statement by the Council on the Management and Treatment of Diseases of the Chest, of the American College of Chest Physicians,⁷ expressed the view that until investigations designed to determine the effectiveness and limitations of the vaccine have been completed the use of BCG vaccine should be limited to investigative studies. An elaborate organization for that purpose actually has been set up by the World Health Organization, with headquarters in Copenhagen.⁸ Currently, WHO is proceeding with a vaccinating program in which several million persons are inoculated annually, for the most part in countries where other means of controlling tuberculosis are deficient. Extended investigation is being given to details of the program, by the WHO research organization, with particular reference to conversion factors in the change from the tuberculin-negative to the tuberculin-positive state, but no analyses have been released at this relatively early date with reference to the value of the method as a protective procedure. Numerous segments

⁵ American Trudeau Society: Statement on BCG, *Am. Rev. Tuberc.* 60: 681-682, 1949.

⁶ Anderson, R. J., and Palmer, C. E.: BCG, *J. A. M. A.* 143: 1048-1051, 1950.

⁷ Council on the Management and Treatment of Diseases of the Chest: The present status of vaccination in tuberculosis control programs, *Dis. of Chest* 19: 110-111, 1951.

⁸ Yuan, I-Chin, and Palmer, C. E.: The WHO Tuberculosis Research Office, *Pub. Health Rep.* 68: 678-686, 1953.

of the total program have been analyzed by sponsors of programs in individual countries, however, and these testify without exception to decreased tuberculosis morbidity and mortality in the vaccinated groups.

Assuming, then, that safety is assured and that the weight of evidence is in favor of the procedure, practicing physicians may properly ask what persons or groups of persons should receive BCG vaccine. In answer to this we may turn again to the Trudeau Society statement. This document recommends its use only in tuberculin-negative persons, and (1) among those persons with more than ordinary exposure to tuberculosis in their professional duties, viz., physicians, nurses and medical students whose work brings them into contact with patients with this disease. The vaccine is recommended (2) for technical personnel, including hospital and laboratory employees, whose work may expose them to direct contact with the tubercle bacillus.

It is recommended (3) for persons unavoidably exposed to infectious tuberculosis in the home. This group is of particular importance to practicing physicians, for in this day of increasing home treatment of tuberculosis by chemotherapy, the problem of protection of non-infected persons residing in the same household as the patient is a critical one. It is suggested (4) that the vaccine be administered to non-infected patients and employees in mental hospitals and other custodial institutions where exposure to tuberculosis is known or believed to be high.

Finally (5), the vaccine is recommended for children and for adults, if they are still uninfected, who belong to population groups believed to have substandard resistance or residing in communities with high tuberculosis mortality. Although the recommendation is not spelled out in this respect, it may be inferred that it refers to Negro groups living in crowded communities, to Indians in unhygienic environments on certain reservations, and to all groups, white or colored, living under poor economic conditions where tuberculosis is rife.

No one of the several such statements in this country touches upon the availability of the vaccine. Actually there is only one manufacturer in the country licensed under the regulations of the National Institutes of Health of the Public Health Service to produce the vaccine for sale and general distribution, viz, The Research Foundation of Chicago. This organization was licensed officially for interstate distribution of the vaccine on fulfillment of the minimum standards set forth by that agency for its production, safety and potency. The vaccine and full directions for its use may be obtained from the Research Foundation by writing to its headquarters at 70 West Hubbard Street, Chicago 10, Illinois. The National Tuberculosis Association has recently coöperated with the Research Foundation in the preparation of a motion picture describing indications for use of BCG vaccine and the manner in which it is administered.*

* The BCG story. 16 mm. motion picture. Color and sound. Produced by the National Tuberculosis Association and Research Foundation (Chicago), 1954.

In two states, New York and Pennsylvania, state services making the vaccine available without cost to physicians practicing within the state are available. Physicians who wish to take advantage of this opportunity for vaccination of individuals or groups may do so by communicating directly with their state health department.

The vaccine is occasionally produced in other laboratories and made available for research. A brief statement on the availability of the vaccine in its three principal centers of production in the United States was published a few years ago in the *American Review of Tuberculosis*.¹⁰

A wide choice exists in the manner of administration of the vaccine. All procedures are employed only after preliminary tuberculin testing to exclude tuberculin reactors. It is rather generally agreed that present knowledge is not adequate to say categorically which is the best vaccination method. The opinion is held in many quarters that a strong reaction to the vaccine, other things being equal, elicits a proportionately high resistance. An intense reaction, however, may be inconvenient, or even alarming, if the regional lymph nodes swell. The discretion of the physician will guide him in his own selection. He will presumably balance convenience for the patient and himself with his views on the theoretically most effective method of administration. Intracutaneous injection of a tenth of a cubic centimeter of an aqueous suspension of the BCG organism is the time-honored procedure, and quantitatively reliable. Several methods of multiple puncture are advocated. A simple scratch method is widely used in mass campaigns in the WHO program. The oral method, which is extensively employed in South America and particularly in Brazil, has few advocates in this country. At the present time there is increasing use of lyophilized organisms, prepared by the "freeze-dry" method, in the inoculated suspension.

Contraindications to use of the vaccine are few. It is not given to persons who react to tuberculin. This is not because of any inherent danger, but because its use is superfluous in those who are already infected. If the vaccine is administered to a person who reacts to tuberculin, response of more or less intensity may occur, which often goes on to ulceration in a week or two. Such a reaction is in essence a severe tuberculin reaction or "Koch phenomenon," and is not dangerous, although annoying.

The vaccine is not given in the presence of acute infectious disease or to patients with disease of the skin in whom any irritation might lead to extension of existing inflammation.

Opinions vary as to its simultaneous administration with other vaccines. Some investigators recommend simultaneous inoculation. Others caution against undue extension of the smallpox vaccination lesion if BCG and smallpox vaccine are administered at the same time in neighboring regions. Unless haste is required, it would seem wise to adopt the conservative course of single administration.

¹⁰ American Trudeau Society: Production and distribution of BCG vaccine in U. S. A., *Am. Rev. Tuberc.* 65: 647-648, 1952.

Early age is not a contraindication. Some of the most impressive results have been recorded in the vaccination of large groups of new born infants.^{11, 12, 13}

Final conclusions on the value of BCG vaccination cannot be reached at the present time. The bulk of present evidence indicates that it is of distinct value in protection against tuberculosis. Its advantages in mass programs appear demonstrated, particularly in communities where standard medical and social methods for reducing the prevalence of the disease are inadequate. The indications for its use in individual practice seem sound and practical. Undoubtedly it will take years to assess its full value, but in the meantime its employment appears not only safe but desirable under the conditions outlined above.

ESMOND R. LONG

¹¹ Rosenthal, S. R., and Leppmann, M.: BCG vaccination in a tuberculosis control program in infants, children and adults, Trans. 49th Annual Meeting, Nat. Tuberc. Assn., 161-168, 1953.

¹² Aronson, J. D., and Sokoloff, M. J.: Reaction to BCG vaccine according to race and age, Trans. 47th Annual Meeting, Nat. Tuberc. Assn., 131-139, 1951.

¹³ Wallgren, A.: Zur Frage der Tuberkulose-Schutzimpfung, Beitr. z. Klin. d. Tuberk. 101: 295-315, 1948.

REVIEWS

Autopsy Diagnosis of Congenitally Malformed Hearts. By MAURICE LEV, M.D. Pathologist and Chief of Research Laboratories, Mount Sinai Hospital of Miami and Associate Professor of Pathology, University of Miami School of Medicine. 194 pages; 16 × 24.5 cm. 1953. Charles C. Thomas, Springfield, Illinois. Price, \$7.50.

This handbook is intended to guide the pathologist in the identification of congenital malformations of the heart at the autopsy table. There is a brief section on the method of opening, dissecting, and examining the heart. There is then a section on abnormalities of individual parts of the heart as they are encountered in dissection, briefly describing the abnormalities. The third part of the book is devoted to pathological complexes and how they may be recognized at autopsy.

The diagrams are good. All of the illustrations are black and white, and would be more useful in color. Embryology is discussed under the various pathologic complexes, rather than as a unified whole. The bibliography is good.

This small volume should be of use to the pathologist in identifying congenital cardiac deformities.

S. S.

Clinical Disorders of the Heart Beat. By SAMUEL BELLET, M.D., Director, Division of Cardiology, Philadelphia General Hospital, and Associate Professor of Cardiology, Graduate School of Medicine, University of Pennsylvania. 373 pages; 17.5 × 26.5 cm. Lea & Febiger, Philadelphia. 1953. Price, \$8.50.

This volume is intended to cover in detail the essential features relating to clinical disorders of the heart beat. Section I is devoted to introductory remarks on the pertinent anatomy and physiology, principles of therapy, and clinical manifestations. Section II is the major part of the book, and deals with the individual arrhythmias in detail. In Section III are descriptions of the arrhythmia in certain clinical states, and in Section IV is a discussion of drugs used in the therapy of arrhythmias.

This book is well organized and clearly and concisely written. The illustrations are good, and the bibliography complete and up-to-date. The author's approach is generally sound, and the descriptions are complete. Therapy is dealt with practically, with frequent reference to fundamental principles.

This text is highly recommended to all who have occasion to diagnose and treat cardiac arrhythmias.

S. S.

Coronary Heart Disease in Young Adults. By MENARD M. GERTLER, M.D., and PAUL D. WHITE, M.D., with the assistance of E. F. BLAND, J. FERTIG, S. M. GARN, J. LERMAN, S. A. LEVINE, H. B. SPRAGUE and N. C. TURNER. 218 pages; 16 × 24 cm. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. 1954. Price, \$5.00.

In 1768, Heberden stated that most of those affected with angina pectoris "were men . . . , and most of them with a short neck, and inclining to be fat." Twelve years later he wrote "I have seen nearly a hundred people with this disorder, out of which number there have been three women" (quoted by White, P. D.: *Heart Disease*, 3rd Edition, 1944). Gertler, White and co-workers, writing in 1954 on coronary heart

disease in young adults, report 97 males and 3 females in their study group, and claim to have demonstrated that the fat, muscular person is most prone to this disease.

The authors selected 100 persons who were under 40 years of age at the time of proved myocardial infarction, had survived it at least six months, and who fulfilled certain other requirements. They were compared with another group of males of similar age, occupation, and ethnic origin. There was also a "matched control group," individually selected for similar body build in addition to other criteria. The coronary group was analyzed clinically, and compared with the controls as regards heredity, race, and especially physique and morphological characteristics. Occupation, "masculinity," endocrine and biochemical and dietary factors were also considered. The authors believe that their study "has made it possible to select those characteristics which occur to the highest degree in coronary heart disease patients and to recognize them as potentially dangerous to any individual who possesses them. . . . It should theoretically be possible to preselect coronary-prone individuals from the population."

One could criticize the study group in that it may not be a representative sample of all young coronary patients (e.g. 27% Jewish; hypertensives not included; 31 of 97 attended college) or that, by including only those who survived an infarction by six months, it excludes those who had the most severe disease. Further, most comparisons are with the unmatched control group rather than the matched control group. The reviewer would hope they are in error, for all of the criteria (sex, body build, morphological characteristics, heredity, serum total cholesterol, serum uric acid, serum total cholesterol/serum lipid phosphorus ratio, CUP index and salivary redox potential) are apparently beyond the influence of the unfortunate "coronary-prone individual." This book seems to emphasize static rather than dynamic factors.

This monograph makes provocative reading, and is of great interest to cardiologists and internists.

S. S.

The Prenatal Origin of Behavior. Porter Lectures, Series 18. By DAVENPORT HOOKER, Ph.D., Sc.D. 143 pages; 14 x 21.5 cm. University of Kansas Press, Lawrence, Kansas. 1952. Price, \$2.50.

This little book is essentially a series of lectures summarizing the findings of many years' work in a most interesting field. Dr. Davenport and his colleagues have set out to survey the origins of behavior and, in particular, the externally visible overt behavior in developing organisms throughout the vertebrate series. They set, as their goal, the establishment of the points of similarity and differences between species, if either existed.

The main contributions that are described in this book deal with the fetal activity in infra-human vertebrates and the sequence of fetal activity events in human development. The painstaking methods necessary to study and correlate the parallel developments in the nervous system and in muscular activity in the fetus are particularly commendable and well described. Even the author recognizes the fact, however, that much remains to be done and that other organs and systems need to be studied with a somewhat similar point of view and goal. The evidence presented in this book indicates that the behavior of vertebrate animals and man has its genesis in the early responses exhibited during the embryonic or fetal period. While there is a basic similarity in the responses of vertebrate organisms to stimulation, it is evident that each order, genus, or species exhibits reactions characteristic of its own group. A reasonably sound foundation has been laid by the work of the author and other investigators upon which future studies in this field may rest. It is a most stimulating book and must be read carefully to be appreciated. If each reader could be privileged to see the excellent set of motion pictures made in conjunction with

some of this work, the book would be even more valuable, and the scope and profundity of this investigative effort would be even more apparent.

F. H. J. F.

First Report on the Geographical and Geological Distribution of Carcinoma in the Netherlands. Volume I: Foundation for the Study of Psycho-Physics. By DR. J. C. DIEHL, Formerly Surgeon-General of the Royal Netherlands Army, and Dr. S. W. TROMP, Geological Consultant to the United Nations, T. A. A. 120 pages; 20.5 x 29 cm. Foundation for the Study of Psycho-Physics, Hofbrouckerlaan 54, Oegstgeest (Leiden), Netherlands. 1953. Price, \$2.10.

This lithoprint is a preliminary report on the geographical and geological distribution of carcinoma in the Netherlands. This project was sponsored by the Foundation for the Study of Psycho-Physics, which was established in the Netherlands in 1950. Psycho-physics is defined as the science which studies all physical and physico-chemical aspects of living phenomena in general. This is a very ambitious summary of the existing widely scattered data on geographical incidence of cancer. It consists mostly of summarized data, tables, and statistical compilations. The scope of the coverage may be indicated by mentioning some of the factors that have been included in the analysis. Influence of soils, water systems, hygienic conditions, geographical isolations, size of municipalities, and rate of growth of municipal populations are some of the items included for analysis. The geographical factors considered include climate, seasons, race, nationality, soil, and others. In the section on "Geophysical Factors," there appear such items as solar radiation and cosmic radiation effects. In general, the booklet appears to be an attempt to survey the literature in order to facilitate formulation of a plan for future investigations. References are numerous and appear to be well chosen. There are several maps to illustrate some of the points of some of the surveys. In general, however, the material does not appear to be well organized and there is no index. It may be of some interest to highly specialized investigators in the cancer field or to those interested in the possible influence of physical environmental forces on the etiology and progress of certain diseases.

F. H. J. F.

Acute Anuria: A Study Based on Renal Function Tests and Aspiration Biopsy of the Kidney. By CLAUS BRUN. 215 pages; 16 x 24 cm. Ejnar Munksgaard, Copenhagen. 1954. Price, D. kr. 30.00.

This edifying work may be loosely divided into three parts. The first six chapters provide an excellent general review of the subject of acute renal insufficiency. The next six chapters present the author's clinical material and his observations on the thirty-two patients comprising it. The third part contains appendices dealing with the technics of renal function tests and renal biopsy, case reports of the thirty-two patients, a pithy summary of the whole work, and a useful bibliography.

In his historical review, the author points out that the entity (now commonly and unfortunately known as lower nephron nephrosis and often regarded as a syndrome of recent recognition) was undoubtedly described by Ziegler in 1885 and Osler in 1892. Subsequent authors up to World War I and German authors during the war also clearly recognized the syndrome ("Verschüttung"). It was then mostly lost to sight until Bywaters and Beall in 1941, after studying air raid injuries in London, revived its memory. Lucké in 1946 reviewed war experiences and suggested the term "lower nephron nephrosis" which has been widely adopted.

From Brun's work and the work of others it is clear that this term is unsatisfactory. By differential renal function tests, Brun has shown that there is protracted and pronounced impairment of glomerular as well as tubular function. In his ma-

terial, moreover, the proximal tubules were more severely affected than the distal, and interstitial changes were particularly prominent. In this treatise, therefore, Brun has introduced the term *acute tubulo-interstitial nephritis*.

From the point of view of etiology, the small series analyzed in this work is remarkably heterogeneous, with acute anuria resulting from sulfonamide therapy, enteritis, the "hepatorenal syndrome," alkalosis with dehydration, hemorrhage, incompatible transfusion, crush injury, mercury poisoning, air embolism with shock, peritonitis with shock, and several other causes. The potential value of needle biopsy of the kidney, which was successful in little more than half the patients, is emphasized by the author who, with Iversen, introduced the technic in 1951.

Apart from minor lapses in idiom, the book is well and clearly written and organized. There are a few minor but unfortunate errors such as the printing of hyper- for hypochloremic on page 66 and an inaccuracy in one of the key references (Bull, Joekes and Lowe, *Lancet* 1949). The book is paper bound and contains no index. It can be highly recommended to anyone interested in the minutiae of acute renal insufficiency. The opening chapters are perhaps of particular value as they afford an excellent and well argued survey of the morbid anatomy, pathogenesis and mechanism of anuria, and the functional pattern of the kidney in this type of acute anuria.

H. J. L. M.

The Biochemistry of Clinical Medicine. By WILLIAM S. HOFFMAN, Ph.D., M.D. 681 pages; 16 × 25 cm. The Year Book Publishers, Inc., Chicago. 1954. Price, \$12.00.

The opening sentence of the preface, "It is the function of a modern book on the biochemistry of clinical medicine to elucidate that portion of the vast array of recently accumulated information in biochemistry that will help the clinician in the practice of medicine," summarizes the scope of this volume very well. The author has succeeded in fulfilling this function without undue emphasis on highly technical explanations or on formulae, although enough of the latter are included when they are necessary to the understanding of the material. The book is more comprehensive than one might expect from the title. The etiology, pathogenesis, clinical course, and principles of treatment are frequently included, particularly in the discussion of those diseases with which the author has had extensive clinical experience.

This volume should prove useful to anyone interested in the application of biochemical knowledge to the practice of medicine.

M. A.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Advances in Internal Medicine. Volume VI. Editors: WILLIAM DOCK, M.D., Long Island College of Medicine, Brooklyn; and I. SNAPPER, M.D., Beth-El Hospital, Brooklyn. 375 pages; 23.5 × 15.5 cm. 1954. The Year Book Publishers, Inc., Chicago. Price, \$10.00.

Cancer: Diagnosis, Treatment, and Prognosis. 2nd Ed. By LAUREN V. ACKERMAN, M.D., Professor of Surgical Pathology and Pathology, Washington University School of Medicine, St. Louis, Mo., etc.; and JUAN A. del REGATO, M.D., Director, Penrose Cancer Hospital, Colorado Springs, Colo., etc. 1,201 pages; 25.5 × 17.5 cm. 1954. The C. V. Mosby Company, Saint Louis. Price, \$22.50.

- Coronary Heart Disease in Young Adults: A Multidisciplinary Study.* By MENARD M. GERTLER, M.D., and PAUL D. WHITE, M.D., with the aid, advice, and editorial assistance of E. F. BLAND, M.D., J. FERTIG, Ph.D., S. M. GARN, Ph.D., J. LERMAN, M.D., S. A. LEVINE, M.D., H. B. SPRAGUE, M.D., and N. C. TURNER, M.Sc. 218 pages; 24 × 16 cm. 1954. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Massachusetts. Price, \$5.00.
- Emergency Treatment and Management.* By THOS. FLINT, JR., M.D., Director, Division of Industrial Relations, Permanente Medical Group, Oakland and Richmond, California, etc. 303 pages; 24 × 16 cm. 1954. W. B. Saunders Company, Philadelphia. Price, \$5.75.
- Expert Committee on Malaria: Fifth Report. World Health Organization Technical Report Series No. 80.* 42 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.
- Funktionelle Röntgendiagnostik der Halswirbelsäule.* By DR. C. BUETTI-BÄUML. 160 pages; 29 × 20 cm. 1954. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 42.-
- Hormones, Health, and Happiness: Glands and Personality.* By WARREN HENRY ORR, M.D. 322 pages; 21.5 × 14.5 cm. 1954. The Macmillan Company, New York. Price, \$4.50.
- Lectures on General Pathology, Delivered at the Sir William Dunn School of Pathology, University of Oxford.* Edited by SIR HOWARD FLOREY, Professor of Pathology. 733 pages; 24 × 16.5 cm. 1954. W. B. Saunders Company, Philadelphia. Price, \$13.00.
- Lectures on the Scientific Basis of Medicine. Volume II, 1952-53. British Postgraduate Medical Federation, University of London.* 420 pages; 22 × 14 cm. 1954. The Athlone Press, University of London; distributed in U. S. A. by John de Graff, Inc., New York. Price, \$6.00.
- Legal Medicine.* Edited by R. B. H. GRADWOHL, M.D., Sc.D., F.A.P.H.A., Commander, M.C., U.S.N.R. (Retired), Director of the Police Laboratory, Metropolitan Police Department, St. Louis, etc. 1,093 pages; 25.5 × 17.5 cm. 1954. The C. V. Mosby Company, Saint Louis. Price, \$20.00.
- Proceedings of the Second National Cancer Conference* (in two volumes). 1,711 pages; 23.5 × 15.5 cm. 1954. Published by the American Cancer Society; available from the Distribution Manager, American Cancer Society, New York. Price, \$7.50 per set.
- Tuberculosis.* By SAUL SOLOMON, M.D., Associate Visiting Physician, Fourth Medical Division, Bellevue Hospital, New York, etc. 310 pages; 21 × 14 cm. 1952. Coward-McCann, Inc., New York. Price, \$3.50.
- You and Your Health.* By EDWIN P. JORDAN, M.D., Executive Director, American Association of Medical Clinics. 296 pages; 21 × 14 cm. 1954. G. P. Putnam's Sons, New York. Price, \$3.95.

COLLEGE NEWS NOTES

AMERICAN COLLEGE OF PHYSICIANS TO USE NATIONWIDE TV CLOSED CIRCUIT TELECAST IN CONNECTION WITH ITS POSTGRADUATE PROGRAM

On Thursday evening, September 23, 1954, from 6:00 P.M. to 7:00 P.M., Eastern Daylight Saving Time, the American College of Physicians will utilize television through a national closed circuit over the Columbia Broadcasting System to carry to its members and their colleagues a SYMPOSIUM ON THE MANAGEMENT OF HYPERTENSION. This telecast is made possible through the coöperation and generous support of Wyeth Laboratories of Philadelphia, and will be the *first nationwide* closed circuit hookup for postgraduate medical education.

The panel of distinguished physicians who will participate includes:

Cyrus C. Sturgis, M.D., F.A.C.P., Presiding
President, American College of Physicians
Professor of Internal Medicine
University of Michigan, Ann Arbor

F. H. Smirk, M.D., F.R.A.C.P.
Professor of Medicine, University
of Otago
Dunedin, New Zealand

R. W. Wilkins, M.D., F.A.C.P.
Chief, Hypertension Clinic
Massachusetts Memorial Hospital,
Boston

Garfield G. Duncan, M.D., F.A.C.P.
Director of the Medical Division
Pennsylvania Hospital, Philadelphia

Edward D. Freis, M.D. (Associate)
Adjunct Clinical Professor of Medicine
Georgetown University, Washington

Professor Smirk is one of the topmost authorities of the world on methonium compounds. He went to New Zealand from England in 1940 to take the Chair of Medicine at the University of Otago. He is a Fellow of the Royal College of Physicians of London and of the Royal Australasian College of Physicians, being the Senior Censor for the latter in New Zealand. He appears on this program as an official representative of the Royal Australasian College of Physicians in connection with an exchange-guest program being arranged between the two Colleges.

A "closed TV circuit" is one by which reception is controlled and not open to the general TV public. This telecast cannot be picked up in the home, but the invited audience must go to the TV receiving station. Twenty-three such receiving stations will be used; these will be located in Boston, New York, Philadelphia, Washington, Pittsburgh, Charlotte, Atlanta, Cincinnati, Detroit, Chicago, St. Louis, Milwaukee, Minneapolis, Memphis, Dallas, Houston, New Orleans, Denver, Salt Lake City, Los Angeles, San Francisco, Baltimore and Cleveland.

Formal invitations have been issued to all members of the College, and to their colleagues, to view and hear this significant program. Each is requested to return the "attendance card" accompanying the invitation, so that adequate facilities will be provided at each station.

GIFTS TO COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College acknowledges with gratitude receipt of the following books, most of which are autographed, that have been presented by member authors:

- Walter Modell, M.D., F.A.C.P., New York City—*The Use of Drugs—A Textbook of Pharmacology and Therapeutics for Nurses*, with Doris J. Place, R.N., and *Handbook of Cardiology for Nurses* (2nd Edition), with Doris R. Schwartz, R.N.
- David Scherf, M.D., F.A.C.P., New York City—*Extrasystoles and Allied Arrhythmias*, with Adolf Schott, M.D.
- James L. McCartney, M.D., F.A.C.P., Garden City, N. Y.—*Frustrated Martyr*.
- Walter B. Shelley, M.D. (Associate), Philadelphia—*Classics in Clinical Dermatology: With Biographical Sketches*, with John T. Crissey, M.D.
- Bernard S. Lipman, M.D. (Associate), Atlanta, Ga.—*Clinical Unipolar Electrocardiography* (2nd Edition), with Edward Massie, M.D., F.A.C.P.
- E. H. Bensley, M.D., F.A.C.P., Montreal, Canada—*Handbook of Treatment of Acute Poisoning*, with G. E. Joron, M.D. (Associate).
- Hans Popper, M.D., F.A.C.P., Chicago, Ill.—*Cardiovascular-Renal Problems, Volume I of Clinical Pathologic Conferences of Cook County Hospital*, with Daniel S. Kushner, M.D.
- Hobart A. Reimann, M.D., F.A.C.P., Beirut, Lebanon—*Pneumonia*.
- Emma Sadler Moss, M.D., F.A.C.P., New Orleans—*Atlas of Medical Mycology*, with Albert L. McQuown, M.D.

MEETINGS, A.C.P. COMMITTEES AND BOARD OF REGENTS

All standing Committees of the American College of Physicians will meet at the College Headquarters in Philadelphia on November 12-13, 1954, and the Board of Regents on November 14, 1954.

The proposals of candidates for membership in the College should be filed sixty days in advance thereof.

All nominations of candidates for the Mead Johnson Postgraduate Scholarships should be filed by October 1, 1954.

All applications for the A. Blaine Brower Traveling Scholarships and the Elizabeth Archbold Bowes Traveling Scholarship should be filed by October 15, 1954.

All matters to be referred to Committees and/or the Board of Regents should be filed with the Executive Secretary by October 15, 1954.

COMING A.C.P. REGIONAL MEETINGS

- ARKANSAS-OKLAHOMA, Oklahoma City, October 8-9, 1954.
- MIDWEST (Illinois, Indiana, Iowa, Wisconsin, Minnesota), Indianapolis, October 9, 1954.
- SOUTHEASTERN (Alabama, Florida, Georgia, South Carolina, Cuba, Louisiana, Mississippi), Edgewater Park, Miss., October 15-16, 1954.
- KENTUCKY, Lexington, October 16, 1954.
- NEW MEXICO, Albuquerque, October 20, 1954.
- NEW ENGLAND (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Eastern Canada), Hartford, October 22, 1954.
- WESTERN PENNSYLVANIA, Pittsburgh, October 27, 1954.
- NEW JERSEY, Newark, November 3, 1954.
- WESTERN NEW YORK, Syracuse, November 19, 1954.
- MICHIGAN, Grand Rapids, December 4, 1954.
- DELAWARE, Wilmington, February 5, 1955.

SOUTHERN CALIFORNIA, San Diego, February 12-13, 1955.

VIRGINIA, Richmond, February 24, 1955.

SOUTHERN ILLINOIS, Peoria, March —, 1955.

KANSAS, Wichita, March 18, 1955.

NORTHERN CALIFORNIA-NEVADA REGIONAL MEETING

The Annual Regional Meeting of the College for Northern California and Nevada was held at San Francisco, June 16, under the Governorship of Dr. Stacy R. Mettler. The Regional Meeting actually occupied one day of a Postgraduate Course, under the auspices of the College, INTERNAL MEDICINE, directed by Dr. Mettler. The attendance at the Regional Meeting consisted of 61 Fellows, 46 Associates or a total of 107 members, plus 61 non-members, or a grand total of 168. In the Postgraduate Course there were registered 22 Fellows, 16 Associates and 44 non-members, or a grand total of 82.

On the evening of the Regional Meeting a reception and dinner was held at the Bohemian Club, with Dr. Mettler acting as Toastmaster. Dr. Loren Roscoe Chandler, Professor of Medicine and formerly Dean of Stanford University School of Medicine, was the guest speaker, his title being "Future Trends in Medicine." Entertainment was arranged by Dr. Roberto F. Escamilla, F.A.C.P. Guests of honor included Dr. Ernest H. Falconer, F.A.C.P., former Regent and former Vice President of the College, Dr. Dwight L. Wilbur, F.A.C.P., Regent of the College, Dr. Theodore L. Althausen, F.A.C.P., Professor of Medicine, University of California Medical School, Dr. Arthur L. Bloomfield, F.A.C.P., Professor of Medicine, Stanford University School of Medicine, Dr. Hans Lissner, F.A.C.P., Clinical Professor of Medicine, University of California Medical School, and Dr. Francis S. Smyth, Dean and Professor of Pediatrics, University of California Medical School. Both the Postgraduate Course and the Regional Meeting were outstanding successes. The excellent attendance attests to the interest and activity of the California members.

COMING EXAMINATIONS BY CERTIFYING BOARDS

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis.

The following oral examination is still to be given:

New York City—Sept. 22-24, 1954.

May 1 was the closing date for the written examination of the Board which will be held Oct. 18, 1954.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Oral Examinations: Chicago, Ill.—Oct. 8-10, 1954.

New Haven, Conn.—Dec. 3-5, 1954.

RESEARCH FELLOWSHIPS OF THE INTERNATIONAL CHILDREN'S CENTRE

A number of fellowships for the academic year 1954-1955 are available for research workers who may wish to work at the Laboratories of the International Children's Centre, Paris. At present the program of research of the Centre is essentially connected with problems of antituberculosis vaccination and anti-pertussis immunization. The grants amount to 60,000 French francs per month. Travelling expenses from their residence to Paris will have to be borne by the research fellows.

Research workers who wish to apply for a fellowship are requested to send their application together with their curriculum vitae, record of previous work, and testimonials of their chiefs of service to Professor Bugnard, International Children's Centre, Château de Longchamp, Paris 16.

A.C.P. RESEARCH FELLOWSHIPS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1955-June 30, 1956. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from \$3,000 to \$3,500.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine St., Philadelphia 4, Pa., and must be submitted in duplicate not later than Oct. 1, 1954. Announcement of awards will be made during November, 1954.

REFRESHER COURSES TO BE GIVEN BY U.S.P.H.S.

Six refresher courses on the laboratory technics of the serology of syphilis and one on the management and control of syphilis serology by the Regional Laboratory will be held at the Venereal Disease Research Laboratory in Chamblee, Ga., from Sept., 1954, through May, 1955, the Public Health Service announced recently.

The six serology courses, each of twelve days' duration, are arranged primarily to meet the needs of senior operating personnel from State laboratories, health departments, Federal Government installations and duly accredited representatives from other countries desiring refresher rather than fundamental training. A course on Management and Control of Syphilis Serology (May 2-13, 1955) by the Regional Laboratory is especially arranged for assistant laboratory directors and senior laboratory staff members.

Reservations will be made as soon as applications are received and lists will be closed one month before the starting date of each course. Correspondence about these courses should be addressed to: Director, Venereal Disease Research Laboratory, Division of Special Health Services, PHS, Department of Health, Education, and Welfare, P. O. Box 185, Chamblee, Ga.

ANNOUNCEMENT OF INSTITUTE

La Rabida Sanitarium, Chicago, announces an annual institute on rheumatic fever on October 11-15, 1954.

The institute will be educational in character and will cover the subject of rheumatic fever and rheumatic heart disease. It will be conducted for four days by members of the hospital staff, together with others selected from the medical schools in this city with which the hospital is affiliated, and by several invited guests. It will be directed primarily to the general practitioner or family physician and to nurses, medical social workers, occupational therapists, dentists and others with a similar interest in the subject. The fifth day, October 15 will be devoted to a scientific program concluding with the Robert A. Black lecture on rheumatic fever.

Advance registration will be required for those who wish to attend the entire five-day session. Attendance will be open to all these groups and will be limited only by the size of the building to accommodate those who attend. Visitors to individual sessions will be admitted by card on previous application.

Further information will be supplied by circular or application to: Institute, La Rabida Sanitarium, East 65th St. and South Shore Drive, Chicago 49, Illinois.

1955 MEETING OF THE AMERICAN PSYCHOSOMATIC SOCIETY

The American Psychosomatic Society will hold its Twelfth Annual Meeting at the Claridge Hotel, Atlantic City, N. J., on May 4-5, 1955. This Meeting will be immediately preceded by those of the American Society for Clinical Investigation and the Association of American Physicians. It will be followed by the meeting of the American Psychoanalytic Association.

The Committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all of the medical specialties, and in contributions in psychophysiology and ecology. Abstracts for the Program Committee's consideration should be submitted in duplicate, and should be sent to the Chairman, Lawrence S. Kubie, M.D., at 551 Madison Ave., New York 22, N. Y.

Dr. Albert F. R. Andresen, F.A.C.P., Brooklyn, N. Y., Clinical Professor of Medicine, Emeritus, State University of New York College of Medicine at New York City, was given the Julius Friedenwald Medal for outstanding achievement in gastroenterology at the annual meeting of the American Gastro-enterological Association in San Francisco, June 19.

Dr. Louis H. Clerf, F.A.C.P., Philadelphia, was presented with the gold medal of the de Roaldes Award at the 75th Annual Meeting of the American Laryngological Association in Boston, May 27-28.

Maj. Gen. Harry G. Armstrong, (MC), USAF, F.A.C.P., former Air Force Surgeon General, was awarded the Distinguished Service Medal by Air Force Chief of Staff, Gen. Nathan F. Twining, in Washington, D. C., July 1. Gen. Armstrong, who is now Surgeon General of the United States Air Force in Europe, was cited for his "exceptional professional and executive ability during his service in Air Force Headquarters from December, 1949, to July, 1954, in supervising preventative and aviation medicine, aeromedical evacuation, and the operation of a world-wide hospital system."

Six members of the College were among those honored for their contributions to the Scientific Exhibits at the A.M.A. annual meeting in San Francisco in June. Dr. Emma S. Moss, F.A.C.P., New Orleans, received, together with Drs. Albert L. McQuown and Robert S. Cooke, the Billings Gold Medal for an exhibit on Fungus Diseases. Dr. S. O. Waife, F.A.C.P., Indianapolis, was a co-recipient of a Certificate of Merit for the exhibit on Glucagon, the Hyperglycemic-Glycogenolytic Factor of the Pancreas in the Section on Experimental Medicine and Therapeutics. In the Section on Internal Medicine, a Certificate of Merit was awarded to Drs. William C. Moloney, F.A.C.P., Boston, and Robert D. Lange (Associate), Minneapolis, Minn., for their exhibit on Late Effects of Irradiation in Atomic Bomb Survivors—Observations on Leukemia and the Eye. Dr. Harold D. Lynch, F.A.C.P., Evansville, Ind., was a co-recipient of a Certificate of Merit for the exhibit on the Submarginal Child in the Section on Pediatrics.

Dr. William A. Brams, F.A.C.P., Chicago, became one of the winners of the American Heart Association's Second Annual Howard W. Blakeslee Awards on Sept. 14 in Washington, D. C. The Blakeslee Awards are given for outstanding reporting in the field of heart and blood-vessel diseases. Dr. Brams received the Award for his book, *Managing Your Coronary*. The Award, which included an honorarium of \$500.00, was presented at a banquet held in conjunction with the Second World Congress of Cardiology and the 27th Scientific Sessions of the A.H.A.

Dr. Alex. M. Burgess, F.A.C.P., Providence, has been appointed official representative of the American College of Physicians on the Medical Advisory Council of the American Occupational Therapy Association. This Council is comprised of physicians representing the medical specialty groups, who will serve as advisors and consultants to the Association. Representatives are being selected from each of the specialties, such as surgery, orthopedics, pediatrics, physical medicine, psychiatry, tuberculosis and internal medicine. Members of the Council may be consulted individually on matters in occupational therapy relating to their particular medical area.

Dr. Carter Smith, F.A.C.P., Atlanta, Governor of the American College of Physicians for Georgia, and Chairman of the Board of Governors, has been appointed by President Cyrus C. Sturgis as the official representative of the American College of Physicians to the Centennial Celebration of Emory University School of Medicine, to be held on October 4-5, 1954.

Dr. I. Frank Tullis, F.A.C.P., Memphis, has been appointed Professor of Medicine and Chief of the Division of Medicine at the University of Tennessee College of Medicine, succeeding the late Dr. Conley Hall Sanford, F.A.C.P.

Dr. Kenneth W. Chapman, F.A.C.P., former Medical Officer in Charge, U. S. Public Health Service Hospital, Lexington, Ky., was transferred in July to Washington, D. C., where he is Chief of the Neuropsychiatric Branch of the Division of Hospitals of the Public Health Service.

Dr. Anthony J. Lanza, F.A.C.P., New York City, has been made Emeritus Professor of Industrial Medicine at New York University Post-Graduate Medical School. Dr. Lanza, who retired at the end of the academic year as Professor and Chairman of the Department of Industrial Medicine and Director of the Institute of Industrial Medicine, New York University-Bellevue Medical Center, will continue to be a consultant in this field.

As of July 1, Dr. Joseph E. Flynn, F.A.C.P., became Professor of Pathology at the University of Missouri School of Medicine, Columbia. Dr. Flynn was formerly Associate Professor of Pathology at Columbia University College of Physicians and Surgeons.

Comdr. John R. Seal, (MC), USN, F.A.C.P., on July 15 became Head of the Communicable Disease Section, Preventive Medicine Division, Bureau of Medicine and Surgery, in Washington, D. C. Comdr. Seal was formerly Officer in Charge and Director of Research at the Naval Medical Research Unit No. 4, Great Lakes, Ill.

Drs. Morris B. Bender, F.A.C.P., New York City, Henry L. Bockus, F.A.C.P., Philadelphia, and Henry A. Schroeder, F.A.C.P., St. Louis, will be the featured guest speakers at the 22nd Annual Assembly of the Omaha Mid-West Clinical Society, to be held Oct. 25-28. Dr. Bender will discuss "Sensory Tests," "Vascular Disease," and "Head Injuries to the Nervous System." He will also lead the discussion of "Management of Neurologic Problems," which will follow the dinner Wednesday evening. Dr. Bockus' topics are "Functional Disorders of the Gastrointestinal Tract," "Role of Aerophagy in Gastrointestinal Symptom Patterns," and "Orientation of Massive Bleeding from Peptic Ulcer—When to Operate." In addition, he will be the discussion leader of "The Role of Roentgenology in Gastroenterology," which

will follow the dinner Monday evening. Dr. Schroeder will speak on "Pathogenesis of Arterial Hypertension," "Drug Treatment of Arterial Hypertension," and "Hazards in the Treatment of Hypertension." He will likewise act as leader for the luncheon discussion of "New Drugs in the Treatment of Hypertension." Twelve members of the College who are members of the Society are also scheduled to make presentations and participate in panel discussions.

Dr. Thomas F. Sellers, Sr., F.A.C.P., Atlanta, Ga., Director of the Georgia Department of Public Health, was the principal speaker at the dedication ceremonies of the new State Hygienic Laboratory in South Charleston, W. Va., on June 26. Dr. Delivan A. MacGregor, F.A.C.P., Wheeling, a former College Governor for West Virginia and Chairman of the State Board of Health, also spoke at the ceremonies.

Dr. Emma S. Moss, F.A.C.P., New Orleans, moderated a Symposium on Diseases Caused by Fungi, sponsored by the College of American Pathologists during the International Congress of Clinical Pathology, held in Washington, D. C., Sept. 6-11.

Dr. Charles F. Wilkinson, Jr., F.A.C.P., New York City, Professor of Medicine and Chairman of the Department at New York University Post-Graduate Medical School, was one of five guest speakers at the Sixth Annual Postgraduate Assembly, sponsored by Saint John's Hospital, Santa Monica, Calif., Sept. 13-15. His subjects were "Spontaneous Hypoglycemia," "The Physiological Basis of Liver Function Tests," and "Recent Advances in the Field of Atherosclerosis."

Drs. Paul György, F.A.C.P., Philadelphia, and Henry T. Ricketts, F.A.C.P., Chicago, are among the featured speakers at the 37th Annual Meeting of the American Dietetic Association, to be held Oct. 26-29 in Philadelphia. Dr. György will discuss "Trends and Advances in Infant Nutrition," and Dr. Ricketts will participate in diet therapy sessions.

Drs. Albert Weinstein, F.A.C.P., Nashville, Tenn., and Morton Hamburger, F.A.C.P., Cincinnati, were among the out-of-state speakers at a seminar sponsored by the Kentucky Chapter of the American Academy of General Practice and held at Kentucky Lake State Park, July 22. Their respective topics were "Peptic Ulcer" and "Recent Advances in Antibiotic Therapy."

In addition to Dr. Samuel Bellet, F.A.C.P., Philadelphia, Dr. David Scherf, F.A.C.P., New York City, also participated in the Seminar on Cardiac Arrhythmias, sponsored by the University of Vermont College of Medicine and the Vermont Heart Association and held in Burlington, Sept. 9-10.

Drs. Irvine H. Page, F.A.C.P., Cleveland, and Robert W. Wilkins, F.A.C.P., Boston, gave presentations on hypertension at the Third International Congress of Internal Medicine, held in Stockholm, Sweden, Sept. 15-18. Dr. Philip S. Hench, F.A.C.P., Rochester, Minn., College Regent, presented a paper on mesenchymal diseases. Also on the program were Drs. William Dameshek, F.A.C.P., and Sara M. Jordan, F.A.C.P., Boston; Dr. Robert M. Stecher, F.A.C.P., Cleveland; Dr. J. A. Barger, F.A.C.P., Rochester, Minn.; Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, College Governor for Michigan; and Dr. T. Grier Miller, F.A.C.P., Philadelphia, College Regent.

Under the Presidency of Dr. Alvis E. Greer, F.A.C.P., Houston, Tex., the American College of Chest Physicians held its Twentieth Annual Meeting in San Francisco, Calif., June 17-20. Thirty-one Fellows and three Associates of the American College of Physicians—representing the United States, Canada, and Mexico—participated in the program; and Dr. Ignacio Chávez, Mexico City, A.C.P. Governor for Mexico, was made an Honorary Fellow at the Annual Convocation on June 19.

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, conducted a Symposium on Liver Disease before the Faculty of Medicine at the University of Brazil in Rio de Janeiro and participated in the Fifth Pan American Conference on Gastroenterology in Sao Paulo, July 19-24.

Drs. E. Cowles Andrus, F.A.C.P., Baltimore, Thaddeus S. Danowski, F.A.C.P., Pittsburgh, and Francis C. Wood, F.A.C.P., Philadelphia, will be among the featured speakers on Friday, Oct. 22, at the annual meeting of the Medical Society of the State of Pennsylvania, to be held in Philadelphia, Oct. 17-22.

Dr. Anton J. Carlson, M.A.C.P., Chicago, and Dr. J. Esben Kirk, F.A.C.P., St. Louis, were recently elected President and Treasurer, respectively, of the Gerontological Society.

Dr. T. F. Sellers, Sr., F.A.C.P., Atlanta, Ga., was recently elected Second Vice President of the newly organized American College of Preventive Medicine at a meeting of the Southern Section of the American Public Health Association in St. Petersburg, Fla. Certification by the American Board of Preventive Medicine will be a prerequisite for membership.

At the annual meeting of the American Diabetes Association, held in San Francisco, June 19-20, Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, Va., was elected President. Dr. Henry T. Ricketts, F.A.C.P., Chicago, was chosen First Vice President, and Dr. Frederick W. Williams, F.A.C.P., New York City, Second Vice President. Dr. John A. Reed, F.A.C.P., Washington, D.C., was elected Secretary.

Meeting in Atlantic City, N. J., in June, the Society of Biological Psychiatry elected Dr. Harold E. Himwich, F.A.C.P., Galesburg, Ill., to the Presidency. Dr. Howard D. Fabing (Associate), Cincinnati, was chosen First Vice President; and Dr. George N. Thompson, F.A.C.P., Los Angeles, was elected Secretary-Treasurer.

Dr. Harry E. Thompson, F.A.C.P., Tucson, Ariz., was chosen President-Elect of the Arizona Medical Association at the recent annual meeting.

Dr. Sidney A. Slater, F.A.C.P., Worthington, Minn., was recently reelected a member of the Board of Directors of the National Tuberculosis Association. Dr. Slater has served on the Board for 24 years, longer than any other member.

Dr. S. M. Poindexter, F.A.C.P., Boise, former A.C.P. Governor for Idaho, has recently been appointed a member of the National Board of Medical Examiners on nomination of the Federation of State Medical Boards. Dr. Poindexter is a member of the Idaho State Board of Medicine and has been its Chairman for the past five years. He was instrumental in preparing a model medical licensure law for Idaho and has shown especial interest in the matter of temporary licensure.

At a recent joint meeting of the Texas Trudeau Society and the Texas Tuberculosis Association, Dr. John W. Middleton, F.A.C.P., Galveston, was elected President.

Drs. Bert E. Mulvey, F.A.C.P., Oklahoma City, Okla., and R. Lee Foster (Associate), Phoenix, Ariz., were recently elected Secretary-Treasurer of their respective state radiological societies.

Dr. S. Fred Strain, F.A.C.P., Memphis, has recently been elected a Vice President of the Tennessee State Medical Association.

Dr. James P. Rousseau, F.A.C.P., Winston-Salem, was recently chosen President-Elect of the Medical Society of the State of North Carolina at its Centennial Meeting; and Dr. Elias S. Faison, F.A.C.P., Charlotte, was elected Second Vice President.

Dr. Jasper A. Smith, F.A.C.P., Waterbury, was recently elected President of the Connecticut Heart Association. Dr. William J. Lahey, F.A.C.P., Hartford, was chosen Vice President. Dr. John C. White, F.A.C.P., New Britain, retiring President, and Dr. S. Allison Rose, F.A.C.P., Stamford, were appointed to the Executive Committee.

Dr. J. Arthur Myers, F.A.C.P., Minneapolis, received the honorary degree of Doctor of Laws at the commencement exercises at Ohio State University, June 13.

Dr. Tully T. Blalock, F.A.C.P., Atlanta, was chosen President-Elect of the Better Health Council of Georgia at its annual business meeting on June 1.

Comdr. Robert E. Switzer, (MC), USN, (Associate), was recently promoted to that rank and was relieved of his duties as Acting Chief of Service and Training Officer for the Neuropsychiatric Service at the U. S. Naval Hospital, National Naval Medical Center, Bethesda, Md., and was assigned as Chief of Neuropsychiatry, U. S. Naval Hospital, Portsmouth, Va.

Dr. Richard V. Ebert, F.A.C.P., formerly of Chicago, on Sept. 1 assumed his new duties as Professor and Chairman of the Department of Medicine at the University of Arkansas School of Medicine, Little Rock.

Dr. William B. Bean, F.A.C.P., Professor of Medicine at the State University of Iowa, served as consultant to the Surgeon General of the U. S. Army in June visiting hospitals in France, Germany and Austria. In July he participated in a Ciba Colloquium on aging in London and visited hospitals and medical schools in England.

Dr. Wyndham B. Blanton, F.A.C.P., Richmond, retired during the summer as Director of the Allergy Clinic at the Medical College of Virginia. His associates in the Clinic, which Dr. Blanton organized in 1936, gave a dinner in his honor and presented him with a silver bowl. Dr. Blanton is continuing as Professor of Clinical Medicine at the College.

Col. Paul Irwin Robinson, (MC), USA, F.A.C.P., has recently been nominated by President Eisenhower for the permanent rank of Brigadier General. Col. Robinson is Eighth Army Surgeon, stationed overseas.

Brig. Gen. James Stevens Simmons, (MC), USA, Retired, F.A.C.P., Boston, received a Distinguished Public Service Award from the Rotary Club of Brookline, Mass., for "achievements and leadership as a scientist, administrator, and educator in the fields of preventive medicine and public health." Gen. Simmons is Dean of the Harvard School of Public Health.

Dr. Herbert Pollack, F.A.C.P., New York City, has recently been appointed Associate Professor of Clinical Medicine at New York University Post-Graduate Medical School. Dr. Pollack is President of the American Diabetes Association, Associate Editor of the *Journal of Metabolism*, and a member of the Editorial Board of the *Journal of Diabetes*.

Dr. Irvin J. Cohen (Associate) has recently been appointed Deputy Director for Hospitals in the Veterans Administration, Washington, D. C. He was previously Manager of the Veterans Administration Hospital in Baltimore.

Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, participated in the Mid-summer Radiological Conference of the Rocky Mountain Radiological Society when it convened in Denver, Aug. 19-21.

Dr. James L. McCartney, F.A.C.P., Garden City, N. Y., spoke on "The Use of Electro-Shock Treatment in the Involutional and Senile Psychoses" at the Third International Congress of Gerontology in London, England, on July 23. On July 24, Dr. McCartney addressed the Third International Congress of Medical Psychotherapy in Zurich, Switzerland, on "The Application of Electro-Shock to Expedite Transference."

Seventy-four members of the College, representing the United States, Canada, and Mexico, are participating in the program of the Second World Congress of Cardiology, being held in Washington, D. C., Sept. 12-17. Dr. Paul D. White, F.A.C.P., Boston, is serving as President of the Congress and is being assisted by Dr. E. Cowles Andrus, F.A.C.P., Baltimore, President of the American Heart Association. Presiding as Chairmen of the symposia and panel discussions are Dr. White, Dr. George E. Burch, Jr., F.A.C.P., New Orleans, Dr. Louis N. Katz, F.A.C.P., Chicago, Dr. Charles E. Kossman, F.A.C.P., New York City, Dr. Samuel A. Levine, F.A.C.P., Boston, Dr. Irvine H. Page, F.A.C.P., Cleveland, Dr. Howard B. Sprague, F.A.C.P., Boston, and Dr. Carl J. Wiggers, F.A.C.P., Cleveland.

ERRATUM

It was erroneously reported in the News Notes Section of the May issue of this journal that Dr. Walter C. Hausheer, F.A.C.P., Staten Island, N. Y., had joined the Medical Department of the Standard Oil Development Company. Dr. Hausheer has been, and still is, Associate Medical Director of the Prudential Insurance Company. It is Dr. Hausheer's son, Dr. Walter T. Hausheer, who has joined the Medical Department of the Standard Oil Development Company.

PROGRESS REPORT—A.C.P. GROUP INSURANCE PLANS

Health and Accident.—The Health and Accident Group Insurance Plan is now closed so far as automatic eligibility of members without regard to health records is concerned. Further applications cannot be accepted unless individually underwritten. This is no disadvantage to the member with acceptable past health record. During the last open subscription period, April 5 to July 15, 1954, 376 additional members obtained policies.

Reports from members who have been disabled indicate that prompt, courteous and efficient service was rendered on their claims. In fact, these reports have been particularly gratifying, concerning the insurance carrier and the College brokers.

The Insurance Company has experienced some trouble due to insured members not promptly reporting, in accordance with regulations of the policy, onset of disability. In some instances, this delay has exceeded six months, whereas notice should be filed with the Association Service Office, 1500 Walnut St., Philadelphia 2, Pa., within twenty-five days from the beginning of a disability. The Insurance Company must, by law, maintain certain reserves. These reserves are computed after taking into consideration the maximum period of notification for a claim notice to reach the Association Service Office. While the Company has not yet refused to accept a late notice, they have the right to do so. It has held up one or two claims pending receipt of information as to the cause of late notice of disability. To assure prompt settlement of claims, insured members must promptly send Notice of Disability to the Association Service Office.

Professional Liability (Malpractice).—This Plan is growing every month. It is quite apparent that malpractice rates are being increased continually by Companies writing individual policies. For example, notice has been received recently that North Carolina has approved a 50% increase in rates, effective August 1, 1954. Rates for the College Plan remain unchanged in North Carolina, as well as in all other areas of the United States.

Certificates have been issued to over 1,000 members of the College; many other members have filed applications for policies to start at a future date. Members are advised to check their renewal rates of their old companies against the rates for the College Plan, thus to be assured of the advantages to be obtained from the College Plan.

Dread Disease.—Almost 1,300 members elected to secure the benefits of this Plan for themselves and families. Many insured their unmarried children who have passed their 21st birthday.

A special announcement about this plan—It has been extended to cover also rabies, tularemia and typhoid fever. These new coverages have been added to the Master Policy delivered to the College. Endorsements have not been sent to each certificate holder, so it is suggested that members attach a memorandum to their certificates of these additions. Naturally all claims for these disabilities will be honored.

The first claim under the Dread Disease Insurance Plan has been filed from Houston, Texas, where a daughter of a College member has contracted encephalitis.

OBITUARIES

DR. MAURICE J. ANSFIELD

Dr. Maurice Joseph Ansfield, F.A.C.P., of Milwaukee, Wis., died of lymphosarcoma on May 27, 1954.

Dr. Ansfield was born in Milwaukee in 1908. He had a distinguished scholastic career at the University of Wisconsin, where he was awarded a B.S. degree in 1930 and an M.D. degree in 1932 with highest honors. His clinical training was acquired at the Milwaukee County Hospital and the Johnston Emergency Hospital, where he served as intern and medical resident from 1932-36. In 1936 he engaged in the private practice of internal medicine in Milwaukee, which he continued most successfully to his untimely death. He was a member of the attending staffs of Mt. Sinai and Milwaukee County Hospitals. From 1938-44 he served as Deputy Superintendent of the Bureau of Contagious Diseases of the Milwaukee Health Department and from 1944-45 as Lieutenant, (MC), USNR. Beginning in 1945 he took an active part in the teaching of clinical medicine and at his death held the rank of Assistant Professor of Clinical Medicine at Marquette University School of Medicine.

Dr. Ansfield was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1952. He was a member of his county and state societies, the American Medical Association, and the Wisconsin and American Heart Associations.

His principal medical interest lay in the field of infectious diseases, which he followed closely and to which he made several clinical contributions. His non-medical interests lay in welfare and religious fields, to which he was deeply devoted.

Dr. Ansfield was a quiet, kindly and scholarly man, the depth of whose intellectual resources was known only to a few of his intimate associates but the warmth of whose heart was known and appreciated by all of his many devoted patients.

FREDERICK W. MADISON, M.D., F.A.C.P.,

Governor for Wisconsin

DR. LOUIS MARK

Dr. Louis Mark, F.A.C.P., was born in Duluth, Minn., Dec. 11, 1890, and died in Columbus, Ohio, of metastatic malignancy on Feb. 25, 1954. He received his medical degree from Marquette University School of Medicine in 1915, serving his internship at the Milwaukee Children's and Cincinnati General Hospitals, 1915-16. From 1918 to 1919, he was Resident at the Cincinnati Tuberculosis Sanatorium and the Ohio Tuberculosis Hospital. Since 1919 he had been Medical Director of the Rocky Glen Sanatorium at McConnelsville, Ohio. Dr. Mark also maintained offices in Columbus, where he was Chief of the Department of Chest Diseases at White Cross Hospital from 1929 to the time of his death. Between 1934 and 1942, he was Medical Director of the Jane M. Case Hospital in Delaware, Ohio. He became a Fellow of the American College of Physicians in 1926 and was an enthusiastic and contributing member to the College for the remainder of his life.

Dr. Mark's chief medical interest was always in the field of tuberculosis and chest diseases. He made many contributions, both oral and written, to the field of his chosen specialty, and was active in local, state, and national societies dedicated to the eradication of tuberculosis. He served as Vice President of the Federation of American Sanatoria and as President, 1950-51, of the American College of Chest

Physicians, while maintaining membership in the Mississippi Valley Medical Society, National Tuberculosis, and Ohio Public Health Associations. During World War II, he was advisor to the Ohio Selective Service.

Dr. Mark was a bridge enthusiast, frequently competing, for recreation, in local, state, and national bridge tournaments. He traveled widely, usually combining a medical objective with a pleasure trip. The Fellows and Associates of the College, in Ohio particularly, will miss his jovial presence and stimulating discussions; and his patients will mourn both a devoted physician and a warm friend. To his surviving family go the sympathy of the entire community which Dr. Mark served personally and professionally, and that of the membership of the American College of Physicians.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. JOHN E. RAUSCHKOLB

Dr. John Edward Rauschkolb was born in Columbus, Ohio, Oct. 19, 1895, and died suddenly April 28, 1954, in Cleveland at the height of his professional career. He received his undergraduate training at Ohio State University, gaining his Bachelor of Arts Degree in 1920. He took his medical degree at Western Reserve University School of Medicine in 1923, interning the following year at the Cleveland City Hospital.

Dr. Rauschkolb chose the specialty of dermatology and syphilology, and was successively Demonstrator in Dermatology, Instructor, Senior Clinical Instructor, and Assistant Clinical Professor of Dermatology and Syphilology at Western Reserve University School of Medicine from 1925 to the time of his death. He was Chief of the Dermatology and Syphilology Service at the Cleveland City Hospital and Dermatologist-in-Charge at St. Alexis Hospital. He was Dermatologist and Syphilologist of the Deaconess Evangelical Hospital. He became President of the Cleveland Dermatological Society in 1936-37, and was Secretary-Treasurer of the same Society in 1941-43. He was President of the Cleveland Academy of Medicine during 1942-43, and Secretary and Treasurer of the American Academy of Dermatology and Syphilology. Dr. Rauschkolb was an active member of the American Dermatological Association, the Society for Investigative Dermatology, and the other usual state and national medical associations. He became a Fellow of the American College of Physicians in 1944 and authored numerous papers in his special field of interest.

Dr. Rauschkolb was loved and respected by friends, patients, and students alike, and exerted an exemplary influence on all those with whom he came in contact.

To Dr. Ruth A. Robishaw, F.A.C.P., the wife of Dr. Rauschkolb, goes the sympathy of a host of friends, both outside and within the American College of Physicians.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. J. J. SINGER

Dr. Jacob Jesse Singer, F.A.C.P., was born in Leeds, England, in 1882 and came to the United States at the age of three.

Dr. Singer graduated from Central High School in St. Louis, Mo., received his B.S. degree from Washington University, and graduated from Washington University School of Medicine in 1904. He interned at St. Louis Female Hospital from

1904 to 1906 and practiced in St. Louis from 1906 to 1937. He was Consultant at the City Infirmary, Lutheran and Jewish Hospitals, and in charge of the Chest Diseases Division at Barnes and St. Louis Children's Hospitals. He took an active interest in the growth of Washington University's School of Medicine and, in 1922-23, he helped form the Chest Clinic at Washington University, which was destined to become one of the prototypes of its kind in the world. He pioneered in developing chest diagnostic methods as coöperative teamwork among surgeons, internists, pathologists, and radiologists, which later proved to be the basis for the present-day Consultative Tumor Boards. Dr. Singer also joined Dr. Evarts Graham during the early pioneering days of Dr. Graham's work in the field of thoracic surgery. He was an Associate Professor of Clinical Medicine, Washington University School of Medicine, from 1926 to 1937.

He moved to California in 1937 to become the Medical Director of the Rose Lampert Graff Foundation, which supported research in chest diseases and offered financial aid to medical students. He was an Associate Professor of Clinical Medicine, University of Southern California School of Medicine (1939-41), Medical Director of Cedars of Lebanon Hospital, and Consultant in Diseases of the Chest at the City of Hope, Duarte. He was the Medical Director of the City of Hope Medical Center from 1941 to 1944.

Dr. Singer was a former President of the St. Louis Trudeau Society, member of St. Louis Medical Society, Missouri State Medical Association, American Medical Association, American Association of Thoracic Surgery, and a Diplomate of the American Board of Internal Medicine. He became a Fellow of the American College of Physicians in 1926. His distinguished career ended with a coronary occlusion on April 13, 1954.

Dr. Singer was author of many publications including the books, *Surgical Diseases of the Chest* by Graham, Singer and Ballou, published in 1935, and his own *Differential Diagnosis of Chest Diseases*, published in 1949. He devoted much of his time in his later years to music and art work. Interestingly, he was a pupil and studied art under his daughter, Burr Singer, the famous portrait painter.

Dr. Singer's kind and pleasant personality furthered his scientific accomplishments, which were impressive both in the Middle and Far West. He contributed a large number of scientific papers to the medical literature, primarily in chest diseases, to which he had devoted his major medical interests.

Dr. Singer's colleagues, patients and friends join his family in mourning his passing.

HOWARD R. BIEMAN, M.D., F.A.C.P.

DR. E. S. SLEDGE

Dr. Edward Simmons Sledge, F.A.C.P., of Mobile, Ala., died March 24, 1954, of a cerebral hemorrhage.

Dr. Sledge was born in Jefferson, Ala., Nov. 8, 1887. He received a B.S. degree from the University of Pennsylvania in 1906, and an M.D. degree from the University of Pennsylvania School of Medicine in 1909, where he was elected to Alpha Omega Alpha. He was married Aug. 6, 1918, to Mary Frank Sturdivant of Selma, Ala.

During World War I, Dr. Sledge served as a member of the Staff of the Surgeon General and in the War Plans Division of the War College. Except for this period, he practiced internal medicine in Mobile from 1909 until the time of his death. Dur-

ing this time, he published numerous medical articles and received many professional honors. Dr. Sledge did the first x-ray work ever done in Mobile, and before the Medical College of Alabama was moved from Mobile, he was an Associate Professor of Neurology.

During his many years of active practice, Dr. Sledge was widely known and recognized as one of the leading and outstanding practitioners of internal medicine in Alabama and the region of the Gulf Coast. He had been a Fellow of the American College of Physicians since 1928. In 1937 he was elected President of the Medical Association of the State of Alabama.

The passing of Dr. Sledge will be mourned by his family, colleagues, patients, and friends.

WILLIAM J. ATKINSON, JR., M.D. (Associate)

DR. ALVIN RANDOLPH SWEENEY

Dr. Alvin Randolph Sweeney, F.A.C.P., Baltimore, Md., died April 17, 1954, of a ruptured aneurysm of the abdominal aorta. He was born in Grand Chenier, La., September 2, 1881, received a portion of his medical training at Vanderbilt University School of Medicine, and obtained his medical degree from Jefferson Medical College of Philadelphia, 1908. He was in private practice at Lake Arthur, La., until February, 1913, when he accepted a commission in the United States Public Health Service as an Assistant Surgeon, and remained on duty with this Service for almost 33 years. He first served at the Ellis Island Immigration Station, New York, then at the New Orleans and Galveston Quarantine Stations and at the St. Louis U. S. Marine Hospital until entry of the United States in World War I, when he assumed command of that installation.

In October, 1917, he was detailed to Extracantonment Zone Duty with the U. S. Army, serving at Camp Bowie, Fort Worth, Tex.; then to Camp Greenleaf, Chattanooga, Tenn., and thereafter to Fayetteville, N. C., as Officer-in-Charge of the Fort Bragg Extracantonment Zone until August, 1919. On the last assignment, he not only acted as Health Officer of the Military Forces, but also carried duties as Health Officer of the City of Fayetteville and of Cumberland County.

Thereafter he filled the following assignments: August, 1919, assigned for duty at U. S. Marine Hospital, Stapleton, N. Y.; October, 1920, detailed for duty at Ellis Island Immigration Station; August, 1923, Medical Officer-in-Charge, St. Louis Marine Hospital; June, 1925, assigned as Medical Officer-in-Charge of the Sabine District Headquarters, Port Arthur, Tex.; February, 1927, Chief, Quarantine Station of the Port of Boston, Mass., embracing Salem, Plymouth, Fall River and New Bedford. His able and humanitarian service was several times honored, including his being elected to a life membership in the Boston Chamber of Commerce. During this time, he was a special lecturer in the Harvard School of Public Health.

In 1935, he was transferred to the Quarantine Station for the Delaware Valley, U. S. A., located at Marcus Hook, Pa., until 1938, when he was detailed as Commanding Officer of the U. S. Marine Hospital, Ellis Island, serving until he transferred as Commanding Officer of the U. S. Marine Hospital, Cleveland, Ohio. He became Medical Director, Ninth Naval District, and became active in several civic activities, including the chairmanship of the Red Cross and Tuberculosis Association Fund Drives until June, 1945. In July, 1945, he became Superintendent of Gallinger Municipal Hospital in Washington, where he served until April, 1949, retiring because of ill health. During this period, he was a member of the Washington Health Council.

Dr. Sweeney was elected a Fellow of the American College of Physicians in 1941. He was a member of the Medical Society of the District of Columbia, the Association of Military Surgeons of the United States and the American Medical Association. He was the author of many articles on health topics, and was known for his contributions to Internal Medicine, Dermatology and Public Health.

DR. WILLARD O. THOMPSON

Dr. Willard Owen Thompson, F.A.C.P., Clinical Professor of Medicine at the University of Illinois College of Medicine, died at the Henrotin Hospital on March 23, 1954, aged 55, of cerebellar hemorrhage secondary to hypertensive cardiovascular disease.

Dr. Thompson was born in Fredericton, N. B., Can., Feb. 17, 1899, and came to the United States in 1920. After graduation from Harvard Medical School in 1923, he served an internship in Boston City Hospital from 1923 to 1925. After several fellowships, Dr. Thompson came to Chicago in 1929 and served in various capacities at the Rush Medical College and the University of Illinois.

From 1930 to 1946 he was an Associate Attending Physician at the Presbyterian Hospital, also serving on the attending staff of Cook County Hospital. Since 1947 he had been an Attending Physician at Grant Hospital, the Henrotin Hospital and, since 1945, at the Research and Educational Hospitals of the University of Illinois.

Dr. Thompson was Editor of the *American Lectures in Endocrinology* and the *Journal of the American Geriatrics Society*, former Editor of the *Year Book of Endocrinology* and, since 1946, Managing Editor of the *Journal of Clinical Endocrinology and Metabolism*. He was on the editorial board of the *Mississippi Valley Medical Journal*, *American Practitioner*, and *GP* and contributed numerous scientific articles to medical publications and textbooks.

He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1931. Dr. Thompson was very active in many medical societies, having held numerous offices, and was a former President of the Chicago Medical Society. In College affairs he was active for a number of years in the Midwest Regional Meetings and also a frequent Director of the Postgraduate Courses in Endocrinology which were sponsored by the College. At the time of his death, Dr. Thompson was the Chairman of the Panel Committee on Endocrinology for the 35th Annual Session of the College in Chicago. He had already done much to put together the program of his Committee.

Dr. Thompson was an enthusiastic teacher, and during his entire professional life took an active part in lecturing before the many societies of which he was a member.

HOWARD WAKEFIELD, M.D., F.A.C.P.,

Governor for Northern Illinois

DR. J. D. WILLIS

Dr. Julius Dreher Willis, F.A.C.P., was born in Floyd County, Va., on Aug. 10, 1886. After a preparatory period at Roanoke College, he graduated in medicine from the Medical College of Virginia in 1909. He began the practice of internal medicine in Roanoke in 1912 and continued in active practice in that city until his death on Jan. 29 of this year. During this entire period he was active in all worthwhile medical endeavors, was a member of the Southwest Virginia Medical Society, Medical Society of Virginia, and Southern Medical Association. He was formerly a Vice

President and Secretary of the Roanoke Academy of Medicine and was a Diplomate of the American Board of Internal Medicine.

Dr. Willis was elected a Fellow of the American College of Physicians in 1922 and had been active in its affairs since that time. He was one of the older Fellows in the state and cherished his membership in this organization. He will be missed because of the influence he exerted on the practice of medicine in Southwest Virginia, and his passing will be felt by those surviving him.

CHARLES M. CARAVATI, M.D., F.A.C.P.,
Governor for Virginia

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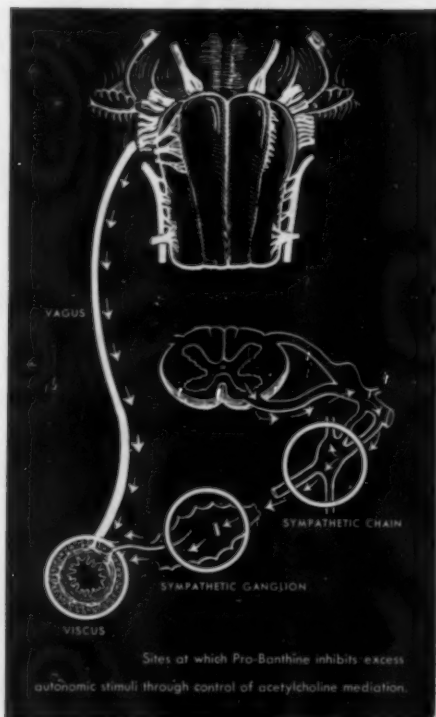
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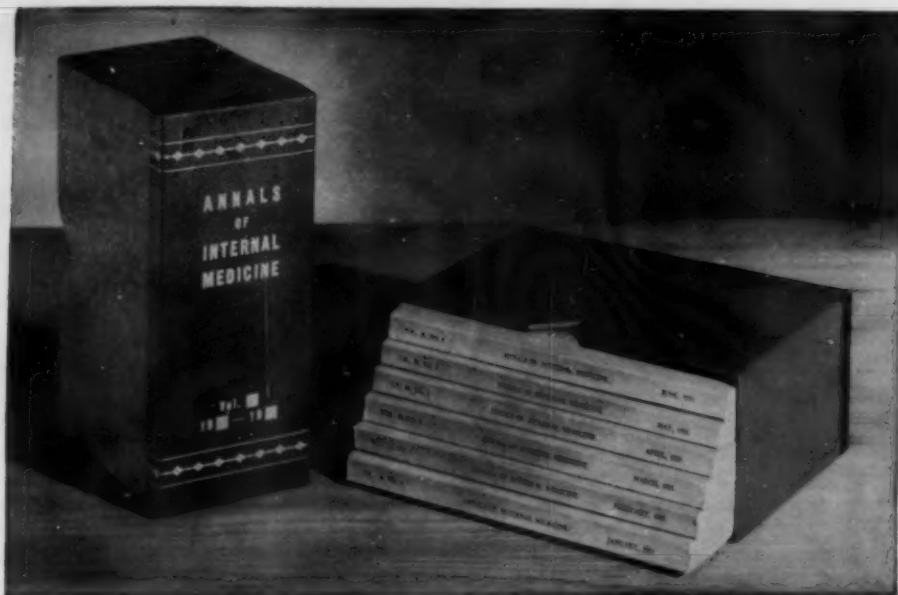
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1. Schwartz I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: *Gastroenterology* 25:416 (Nov.) 1953.

2. Roback, R. A., and Beal, J. M.: *Gastroenterology* 25:24 (Sept.) 1953.



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85:132 (Jan. 1950)

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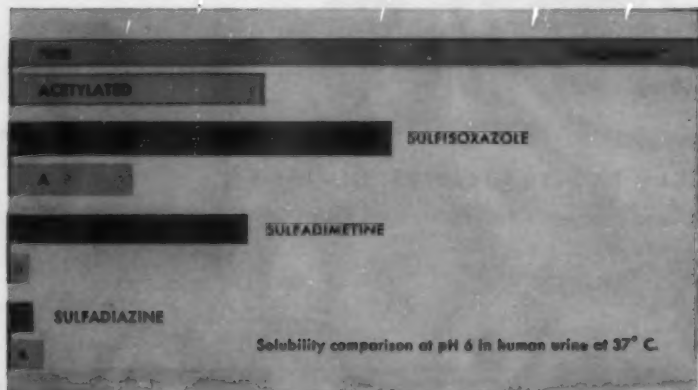
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	October				November				December				
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(All registrations must be made through the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa. Fees: A.C.P. Members, \$30.00; non-members, \$60.00. Registration forms and detailed bulletins furnished on request.)								Thanksgiving, November 25					
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Course No. 2, BASIC CONCEPTS IN INTERNAL MEDICINE ; Medical College of Virginia, Richmond, Va.; Charles M. Caravati, M.D., F.A.C.P., and Kinloch Nelson, M.D., F.A.C.P., Co-Directors.		11-15											
Course No. 3, NEWER DEVELOPMENTS IN CARDIOVASCULAR DISEASES ; Mount Sinai Hospital, New York, N. Y.; Arthur M. Master, M.D., F.A.C.P., and Charles K. Friedberg, M.D., F.A.C.P., Co-Directors.		11-15	18-22										
Course No. 4, MEDICAL ASPECTS OF NEOPLASTIC DISEASES ; Memorial Center for Cancer and Allied Diseases, New York, N. Y.; Cornelius P. Rhoads, M.D., F.A.C.P., and Rulon W. Rawson, M.D., F.A.C.P., Co-Directors.				X									
Course No. 5, SELECTED SUBJECTS IN INTERNAL MEDICINE ; University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Roy R. Snowden, M.D., F.A.C.P., Director; Frank J. Gregg, M.D., F.A.C.P., Co-Director.					1-5	8-12							
Course No. 6, PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE ; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Julius H. Comroe, Jr., M.D., F.A.C.P., Director.													
Course No. 7, INTERNAL MEDICINE ; Beth Israel Hospital, Boston, Mass.; Herrman L. Blumgart, M.D., F.A.C.P., Director.													
Course No. 8, GASTRO-ENTEROLOGY ; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; Henry L. Bockus, M.D., F.A.C.P., Director.													
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1. Editorial, *J. Allergy* 23: 279, 1952.



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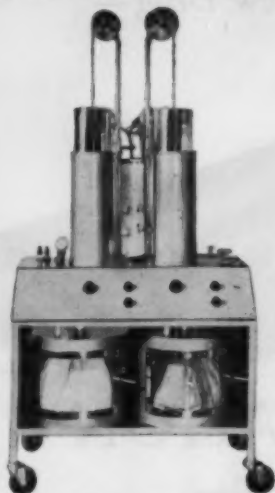
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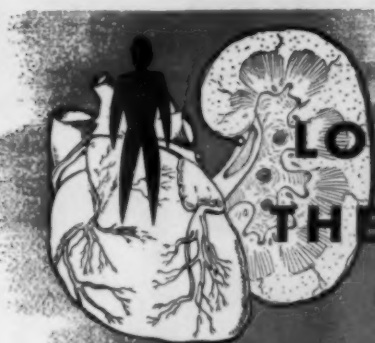
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Average sodium —
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Meat, 1 serving
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Low sodium bread
Cereal
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liquefied — to be
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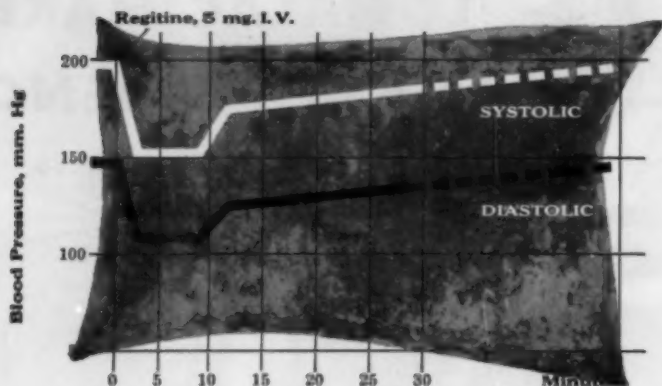
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one curable form of hypertension



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(phentolamine methanesulfonate CIBA)

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1. DECHOUROY, J. L. I AM. J. SURG., 86:37, JULY, 1953

C I B A Summit, New Jersey

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simplifies control of edema

CARBO-RESIN

(Carboxystyrene Resin, Lilly)

safely prevents the absorption of
sodium . . . permits a more palatable diet

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